

American Journal
of
Digestive Diseases
Volume 13

The American Journal of

DIGESTIVE DISEASES

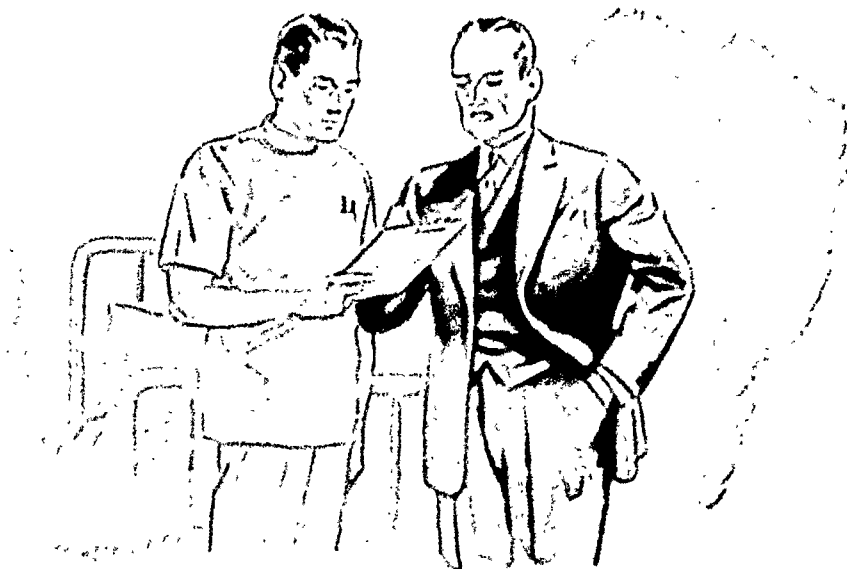
An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

MANAGEMENT OF CHRONIC CONSTIPATION — <i>Michael H. Streicher, M.D.</i>	1
MODERN CONCEPT OF CONGENITAL MEGACOLON — <i>Eduard Muehsam, M.D.</i>	3
SOME DERMATOLOGIC ASPECTS OF ALLERGY — <i>John A. Turnbull, M.D.</i>	9
DIVERTICULA OF THE COLON VERSUS GALLSTONES — <i>Arnold Galambos, M.D., and Wilma Mittelman-Galambos, M.D.</i>	14
GASTRIC CARCINOMA: REVIEW OF ERRORS IN DIAGNOSIS — <i>Meyer Golob, M.D.</i>	17
CLINICAL EVALUATION OF THE LABORATORY TESTS OF THE STOMACH — <i>Rudolf Ehrmann, M.D.</i>	23
HEREDITY, AN IMPORTANT FACTOR FOR THE EARLY DIAGNOSIS OF GASTRO- INTESTINAL CANCER — <i>Rudolf Ehrmann, M.D.</i>	25
OBITUARY — <i>Mills Sturtevant, M.D.</i>	25
ABSTRACTS OF CURRENT LITERATURE —	26

872



WHEN NUTRITION MUST BE MAINTAINED

Few are the diseases in which maintenance of the nutritional state is less important than specific therapy. For unless the metabolic demands are adequately satisfied, maximal response to drug administration hardly can be expected.

In a host of febrile, infectious, and neoplastic diseases Ovaltine can be of considerable benefit in supplying the extra nutrients required during periods of greater need. This nutritious food

drink, made with milk, supplies the dietary elements required: adequate protein, readily assimilated carbohydrate, B complex and other vitamins, as well as important minerals. Ovaltine leaves the stomach rapidly because of its low curd tension, hence may be taken as frequently as deemed necessary. And its delicious taste encourages adequate consumption, an important factor in combating the anorexia of many diseases.

THE WANDER COMPANY, 360 NORTH MICHIGAN AVENUE, CHICAGO 1, ILLINOIS



Ovaltine

Three daily servings of Ovaltine, each made of ½ oz. Ovaltine and 8 oz. of whole milk,* provide:

PROTEIN	31.2 Gm.	VITAMIN A	2953 I.U.
CARBOHYDRATE	62.43 Gm.	VITAMIN D	430 I.U.
FAT	29.34 Gm.	THIAMINE	1.296 mg.
CALCIUM	1.104 Gm.	RIBOFLAVIN	1.273 mg.
PHOSPHORUS503 Gm.	NIACIN	7.0 mg.
IRON	11.94 mg.	COPPER5 mg.

*Based on average reported values for milk.

The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

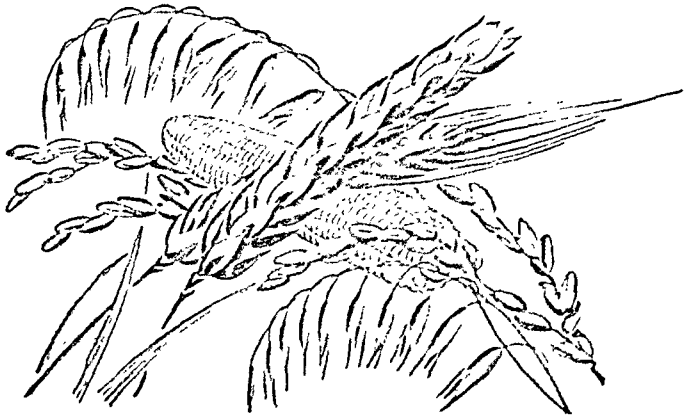
ORIGINAL CONTRIBUTIONS

CARCINOGENIC VALUE OF OXIDATED OILS — <i>Prof. Angel H. Roffo</i>	33
INCIDENCE OF APPENDICITIS FROM A SURVEY OF COLLEGE STUDENTS — <i>Karl A. Stiles, Ph.D. and Frederick W. Mulsow, M.D.</i>	39
ENDOCRINE ASPECTS OF OBESITY — <i>Max A. Goldzieher, M.D.</i>	40
ABSTRACTS OF CURRENT LITERATURE	55

Volume 13

February, 1946

Copyright 1946, The Sandfield Publishing Co.



Few Other Foods Can Better This Nutritional Composition

During the recent past much has been learned about nutritional needs. The importance of an adequate morning meal has gained wide recognition. That breakfast should be adequate not only calorically, but also in its content of essential nutrients, is advocated by medical as well as nutritional authorities.

In the breakfasts recommended, cereals, ready to eat or to be cooked, occupy an important place. For there are few foods that can better the nutritional composition of the dish composed of cereal, milk, and sugar.

Besides quickly available food energy, this dish provides notable amounts of biologically adequate protein, the essential B vitamins

thiamine, riboflavin, and niacin, and important minerals.

The nutritional contribution made by 1 oz. of cereal (whole-grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of milk, and 1 teaspoonful of sugar, is shown in this table of composite averages:

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

★

★

★

The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

PROTEIN DEFICIENCY IN MAN — <i>Melville Sabyun, Ph.D.</i>	59
ABDOMINAL PAIN IN PNEUMONIA — <i>Harry Gauss, M.D.</i>	73
THE PHYSIOLOGIC USE OF WATER IN CONSTIPATION — <i>James A. McKenney, M.D.</i>	78
VITAMINS AND HORMONES IN NUTRITION. II. ENDOCRINE DYSCRASIA — <i>Benjamin F. Sieve, M. D.</i>	80
REDUNDANCY OF THE COLON — <i>Arnold Galambos, M.D. and</i> <i>Wilhelmina Mittelman Galambos, M.D.</i>	87
EDITORIAL: SILENT GALLSTONES	101
ABSTRACTS OF CURRENT LITERATURE	103

March, 1946

Number 3

946, The Sandfield Publishing Company



WHEN *Living Itself* PROVES DIFFICULT

Stamina and strength, essential to a joyous, optimistic outlook, are vitally linked to the nutritional status, and will quickly wane if undernutrition is allowed to develop. Zestful living and boundless energy are hardly compatible with nutritional deficiencies.

For the below-par patient whose inadequate nutritional intake is the responsible factor, Ovaltine as a dietary supplement can make a real contribution toward assuring nutritional balance. A good source of high-quality pro-

tein, readily utilized carbohydrate, well-emulsified fat, and essential vitamins and minerals, Ovaltine can prove a significant factor in restoring the desired state of optimal nutrition. Three glassfuls daily, made with milk as directed, provide appreciable amounts of essential nutrients as indicated by the table. The low curd tension of Ovaltine assures rapid gastric emptying, hence the appetite for regular meals is not impaired. Ovaltine is equally enjoyed with meals and between meals.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



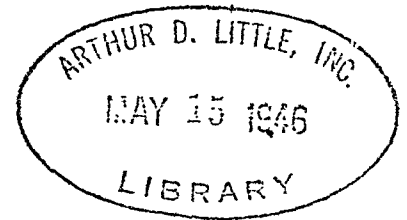
Ovaltine

Three daily servings of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk,* provide.

CALORIES	659	VITAMIN A	3300 I.U.
PROTEIN	32.1 Gm	VITAMIN B ₁	1.16 mg
FAT	31.5 Gm	RIBOFLAVIN	1.50 mg
CARBOHYDRATE	64.8 Gm	NIACIN	6.81 mg
CALCIUM	1.12 Gm	VITAMIN C	39.6 mg
PHOSPHORUS	0.939 Gm	VITAMIN D	417 I.U.
IRON	12.0 mg	COPPER	0.75 mg

*Based on average reported values for milk.

The American Journal of DIGESTIVE DISEASES

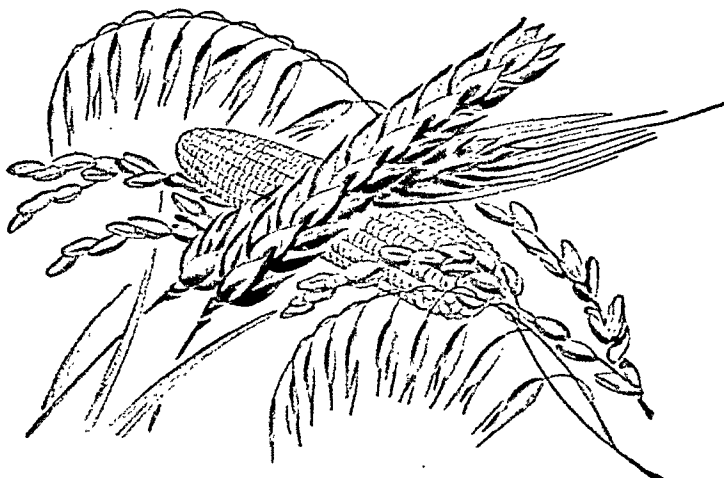


An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

THE ISOLATION AND TESTING OF FECAL STREPTOCOCCI — <i>George H. Chapman</i>	105
A METHOD FOR BIO-ASSAY OF EXTRACTS WHICH INHIBIT GASTRIC SECRETION — <i>M. H. F. Friedman, M.D. and D. J. Sandweiss, M.D.</i>	108
THE ROLE OF THE COENZYMES OF THE B COMPLEX VITAMINS AND AMINO ACIDS IN BALANCED NUTRITION — <i>Simon L. Ruskin, M.D.</i>	110
BOOK REVIEW: NUTRITION AND CHEMICAL GROWTH IN CHILDHOOD — <i>Icie G. Macy, Ph.D., Sc.D.</i>	122
ABSTRACTS OF CURRENT LITERATURE	123



Breakfast and the Convalescent Ulcer Diet

After the acute phase of peptic ulcer has subsided and dietary liberalization is possible, maintenance of the improved status becomes the objective of therapy. The convalescent ulcer diet, begun at this time, provides bland and easily digested foods to evoke minimum gastric juice secretion and peristaltic activity, and to induce maximal neutralization of the acid gastric juice.

Because of the frequency of meals and the need for preventing complete emptying of the stomach, a relatively substantial breakfast must be provided in the convalescent ulcer diet. Cereals have always been an important component of this meal. Thoroughly bland—except those purposely made different through inclusion of bran—they are digested with a minimum of effort, and do not stimulate undue acid secretion or peristalsis. Furthermore, cereals are eaten

with milk or cream, both of which are essential in ulcer management.

The wide variety of cereals, both in taste and physical consistency, permits variations in meal planning, thus avoiding monotony of diet. This table of composite averages indicates the nutritional contribution made by the serving of 1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar.

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

The American Journal of DIGESTIVE DISEASES

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

THE USE OF CARBOHYDRATE IN DIABETIC ACIDOSIS — <i>John P. Peters, M.D.</i>	127
WHAT IS THE CAUSE OF DIABETES MELLITUS IN MAN? — <i>I. Arthur Mirsky, Major, M.C., U. S. A.</i>	130
SURGERY OF THE ACUTE ABDOMEN IN PATIENTS WITH DIABETES MELLITUS — <i>Beverly Chew Smith, M.D.</i>	138
MEDICAL MANAGEMENT OF THE DIABETIC PATIENT DURING AN ACUTE ABDOMINAL EMERGENCY — <i>Louis Bauman, M.D.</i>	140
RECENT ADVANCES IN THE MANAGEMENT OF GANGRENE AND INFECTIONS IN PATIENTS WITH DIABETUS MELLITUS — <i>Leland S. McKittrick, M.D.</i>	142
A QUARTER OF A CENTURY IN MEDICAL RESEARCH — <i>Charles H. Best, C.B.E., F.R.S.</i>	148
CARBOHYDRATE METABOLISM IN TRAUMATIC SHOCK — <i>R. E. Haist, M.D., Ph.D.</i>	152
FACTORS AFFECTING FAT TRANSPORT IN THE ANIMAL BODY — <i>Charles H. Best, C.B.E., F.R.S.</i>	155
EVALUATION OF BLOOD SUGAR TESTS — <i>Herman O. Mosenthal, M.D.</i> <i>and Eileen Barry, B.S.</i>	160
EDITORIAL:	
THE CAUSE OF DIABETES IN MAN	170
WHEN SHALL WE USE GLUCOSE IN COMA?	170
ACTA CLINICA BELGICA	171
OBITUARY — <i>Henry Kendall, M.D.</i>	171
BOOK REVIEWS:	
ROENTGEN DIAGNOSIS OF DISEASES OF THE GASTRO-INTESTINAL TRACT	172
MEMOIRS OF WALTER REED: THE YELLOW FEVER EPISODE	172
ESSENTIALS OF HISTOLOGY	172
THE PHYSIOLOGY OF THE NEWBORN	172

(Diabetes Number)



In the Nutrition Problems of **CHRONIC CHOLECYSTITIS**

Because of the low fat intake which is frequently necessary, many foods and beverages are denied the patient with chronic gallbladder disease. If dietary curtailment becomes too drastic, however, nutritional deficiencies are apt to develop, adding further complications and physical discomfort.

The delicious food drink prepared by mixing Ovaltine with skim milk provides many of the nutrients considered essential in hepato-

biliary disease, without appreciably increasing the fat intake. Its biologically adequate protein, readily utilized carbohydrate, B complex and other vitamins, as well as essential minerals aid in satisfying the need for these nutrients. This food supplement makes a nutritionally excellent as well as delicious component of the extra feedings which are frequently required in the management of chronic cholecystitis.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



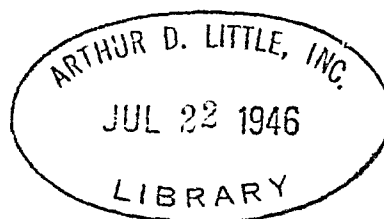
Ovaltine

Three servings daily of Ovaltine, each made of
 $\frac{1}{2}$ oz. of Ovaltine and 8 oz. of skim milk*, provide:

CALORIES	426	VITAMIN A	2058 I.U.
PROTEIN	32.3 Gm.	VITAMIN B ₁	1.16 mg.
FAT	2.5 Gm.	RIBOFLAVIN	1.55 mg.
CARBOHYDRATE	66.3 Gm.	NIACIN	6.81 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
PHOSPHORUS	0.939 Gm.	VITAMIN D	400 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for skim milk.

The American Journal of **DIGESTIVE DISEASES**



An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

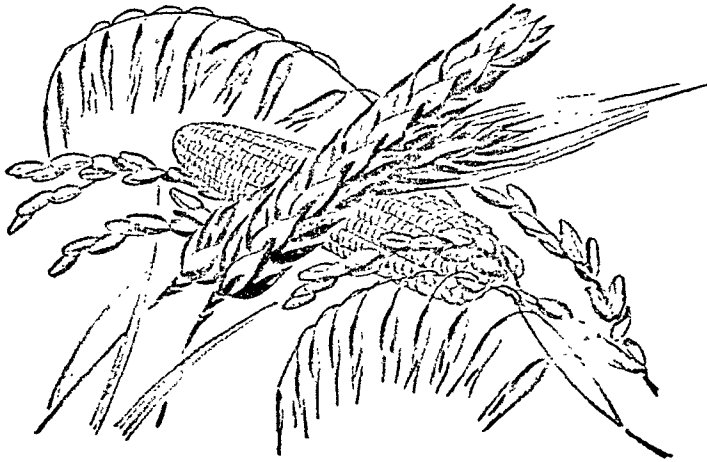
DIET IN UNCONTROLLED DIABETES PRECEDING ACUTE NEUROPATHY — <i>Howard F. Root, M.D. and Clovis Cruz Mascarenhas, M.D.</i>	173
FASTING BLOOD SUGAR VERSUS POST-PRANDIAL BLOOD SUGAR — <i>Anthony Sindoni, Jr., M.D.</i> ..	178
SUDDEN AND DRASTIC CHANGES OF THE CARBOHYDRATE TOLERANCE IN SEVERE INSULIN-TREATED DIABETES — <i>Arnold Galambos, M.D. and</i> <i>Wilhelmina Mittelman-Galambos, M.D.</i>	193
THE CONTROL OF DIARRHEA BY TOMATO POMACE — <i>Lester M. Morrison, M.D.</i>	196
EXPERIENCES IN NON-SPECIFIC DIARRHEAL CONDITIONS IN THE EUROPEAN THEATER OF OPERATIONS — <i>William J. Hanes, Major, M. C.</i>	199
EDITORIAL:	
HISTORY OF MEDICINE	210
ABSTRACTS OF CURRENT LITERATURE	211

Volume 13

June, 1946

Number 6

Copyright 1946, The Sandfield Publishing Company



Meal Organization and the Spastic Colon

Dietary management is one of the principal features of the regimen designed to correct the spastic colon. Not only is the choice of food important, but regularity of eating must be maintained as well. Peristaltic intestinal reflexes, influencing the small and the large bowel, come into operation on eating, and can play an important role in re-establishing spontaneous, normal defecation. Hence three well-balanced meals daily, in contrast to less frequent or more frequent eating, prove most desirable.

Cereals offer many advantages in the dietary of spasticity of the colon. Except for those purposely made different through the inclusion of bran, they are thoroughly bland, and are digested with virtually no remaining irritant residue. Served with milk and sugar, they provide an abundance of essential nutrients, contributing significant amounts of protein, carbohydrate, fat, vitamins and minerals.

Cereals are not only an excellent com-

ponent of the breakfast, but also serve as a source of bland food for one or both of the other meals. Available in a wide variety of taste and physical form, cereals are of universal appeal. Nutritionally, they are equally advantageous whether of the ready-to-eat or to-be-cooked variety. The table of composite averages indicates the nutritional composition of the average cereal serving containing 1 oz. of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 oz. of milk, and 1 teaspoonful of sugar.

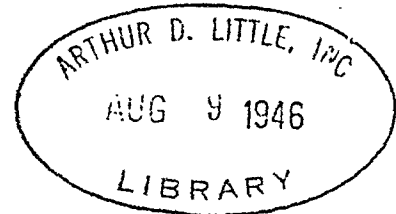
Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

The American Journal of DIGESTIVE DISEASES



An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

PRESENT TRENDS IN MUCOUS COLITIS — <i>Harry Gauss, M.D.</i>	213
AN OUTLINE FOR THE TREATMENT OF PEPTIC ULCER — <i>Earl Parsons Lasher, Jr., M.D.</i>	221
STUDIES OF THE EFFECTS OF HIGH LIPID DIETS ON INTESTINAL ELIMINATION — <i>Helen L. Wikoff, Ph.D., Warren R. Hoffman, B.A. and Jean Caul, Ph.D.</i>	228
BENIGN ULCER OF THE CAECUM — <i>C. D. L. Cromar, Major, RCAMC</i>	230
THE CORRELATION OF INTESTINAL PROTOZOA AND ENTERIC MICRO-ORGANISMS OF KNOWN AND DOUBTFUL PATHOGENICITY — <i>Oscar Felsenfeld, M.D., M.S. and Viola Mae Young, M.S.</i>	232
JEJUNAL CANCER — A CASE REPORT — <i>Imre Braun, M.D.</i>	234
MEDICAL MANAGEMENT OF PYLORIC OBSTRUCTION RESULTING FROM PEPTIC ULCER — <i>Samson A. Seley, M.D.</i>	237
BOOK REVIEWS:	
THE VENOUS PULSE AND ITS GRAPHIC RECORDING — <i>Franz M. Groedel</i>	243
ESSENTIALS OF CLINICAL PROCTOLOGY — <i>Manuel G. Spiesman</i>	244



ALL THE NUTRIENTS

Essential for a Food Supplement

Whenever the intake of essential nutrients must be augmented, as in convalescence from surgery or infectious disease, or in the correction of malnutrition, the delicious food drink which results from mixing Ovaltine with milk can be of significant value. This palatable food supplement provides a wealth of essential nutrients in a pleasant, easily assimilated form. It supplies protein of high biologic value, readily metabolized

carbohydrate, easily emulsified fat, ascorbic acid, B complex and other vitamins, as well as essential minerals. Three glassfuls daily sharply augments the intake of these nutrients, as shown by the table of composition. Its low curd tension makes for rapid gastric emptying, hence appetite for the next meal is not interfered with. This delicious food drink is enjoyed both as a mealtime beverage and between meals.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk*, provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B ₁	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	1.50 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.81 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
PHOSPHORUS	0.939 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

The American Journal of DIGESTIVE DISEASES

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

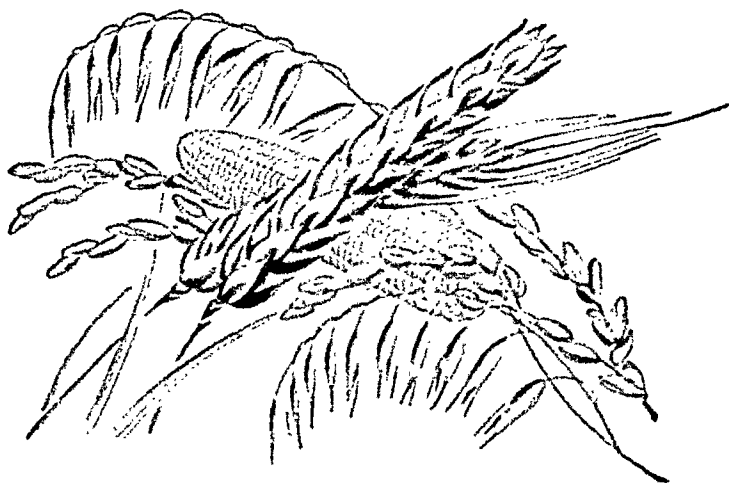
SOME EFFECTS OF GUM CHEWING ON GASTRIC ACIDITY IN HEALTHY INDIVIDUALS — <i>Clayton S. Smith, M.D., Helen L. Wikoff, Ph.D. and Martha E. Southard, B.A.</i>	245
TYROTHRICIN IN PROCTOLOGY — <i>Alfred J. Cantor, M.D.</i>	247
RADIATION THERAPY OF THE CANCER OF THE ESOPHAGUS — <i>J. Borak, M.D.</i>	249
CONTINUOUS DRIP TREATMENT FOR CHRONIC ULCERATIVE COLITIS — <i>Juan Nasio, M.D.</i> ..	252
BRIEF PSYCHOTHERAPY IN THE TREATMENT OF GASTRO-INTESTINAL DISORDERS — <i>Malcolm L. Hayward, M.D.</i>	255
GASTRO-INTESTINAL SYMPTOMATOLOGY IN SCHIZOPHRENIA — <i>Jerome M. Schneck, M.D.</i>	257
PEPTIC ULCER. A ROENTGENOLOGICAL, LABORATORY, AND CLINICAL FOLLOW-UP OF 200 PEPTIC ULCERS — <i>A. J. Delario, M.D.</i>	260
EDITORIAL: PROCTOLOGY AND GASTROENTEROLOGY —	270
BOOK REVIEW: DIABETES — <i>Henry J. John, M.D.</i>	271
ABSTRACTS OF CURRENT LITERATURE	271

Volume 13

August, 1946

Number 8

Copyright 1946, The Sandfield Publishing Company



Breakfast and the Convalescent Ulcer Diet

After the acute phase of peptic ulcer has subsided and dietary liberalization is possible, maintenance of the improved status becomes the objective of therapy. The convalescent ulcer diet, begun at this time, provides bland and easily digested foods to evoke minimum gastric juice secretion and peristaltic activity, and to induce maximal neutralization of the acid gastric juice.

Because of the frequency of meals and the need for preventing complete emptying of the stomach, a relatively substantial breakfast must be provided in the convalescent ulcer diet. Cereals have always been an important component of this meal. Thoroughly bland—except those purposely made different through inclusion of bran—they are digested with a minimum of effort, and do not stimulate undue acid secretion or peristalsis. Furthermore, cereals are eaten

with milk or cream, both of which are essential in ulcer management.

The wide variety of cereals, both in taste and physical consistency, permits variations in meal planning, thus avoiding monotony of diet. This table of composite averages indicates the nutritional contribution made by the serving of 1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar.

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

The American Journal of DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

THE USE OF CARBOHYDRATE IN DIABETIC ACIDOSIS — <i>John P. Peters, M.D.</i>	127
WHAT IS THE CAUSE OF DIABETES MELLITUS IN MAN? — <i>I. Arthur Mirsky, Major, M.C., U. S. A.</i>	130
SURGERY OF THE ACUTE ABDOMEN IN PATIENTS WITH DIABETES MELLITUS — <i>Beverly Chew Smith, M.D.</i>	138
MEDICAL MANAGEMENT OF THE DIABETIC PATIENT DURING AN ACUTE ABDOMINAL EMERGENCY — <i>Louis Bauman, M.D.</i>	140
RECENT ADVANCES IN THE MANAGEMENT OF GANGRENE AND INFECTIONS IN PATIENTS WITH DIABETUS MELLITUS — <i>Leland S. McKittrick, M.D.</i>	142
A QUARTER OF A CENTURY IN MEDICAL RESEARCH — <i>Charles H. Best, C.B.E., F.R.S.</i>	148
CARBOHYDRATE METABOLISM IN TRAUMATIC SHOCK — <i>R. E. Haist, M.D., Ph.D.</i>	152
FACTORS AFFECTING FAT TRANSPORT IN THE ANIMAL BODY — <i>Charles H. Best, C.B.E., F.R.S.</i>	155
EVALUATION OF BLOOD SUGAR TESTS — <i>Herman O. Mosenthal, M.D.</i> <i>and Eileen Barry, B.S.</i>	160
EDITORIAL:	
THE CAUSE OF DIABETES IN MAN	170
WHEN SHALL WE USE GLUCOSE IN COMA?	170
ACTA CLINICA BELGICA	171
OBITUARY — <i>Henry Kendall, M.D.</i>	171
BOOK REVIEWS:	
ROENTGEN DIAGNOSIS OF DISEASES OF THE GASTRO-INTESTINAL TRACT	172
MEMOIRS OF WALTER REED: THE YELLOW FEVER EPISODE	172
ESSENTIALS OF HISTOLOGY	172
THE PHYSIOLOGY OF THE NEWBORN	172

(Diabetes Number)

Volume 13

May, 1946

Number 5

Copyright 1946, The Sandfield Publishing Company



In the Nutrition Problems of **CHRONIC CHOLECYSTITIS**

Because of the low fat intake which is frequently necessary, many foods and beverages are denied the patient with chronic gallbladder disease. If dietary curtailment becomes too drastic, however, nutritional deficiencies are apt to develop, adding further complications and physical discomfort.

The delicious food drink prepared by mixing Ovaltine with skim milk provides many of the nutrients considered essential in hepato-

biliary disease, without appreciably increasing the fat intake. Its biologically adequate protein, readily utilized carbohydrate, B complex and other vitamins, as well as essential minerals aid in satisfying the need for these nutrients. This food supplement makes a nutritionally excellent as well as delicious component of the extra feedings which are frequently required in the management of chronic cholecystitis.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



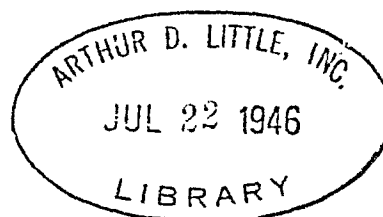
Ovaltine

Three servings daily of Ovaltine, each made of
½ oz. of Ovaltine and 8 oz. of skim milk*, provide:

CALORIES	426	VITAMIN A	2053 I.U.
PROTEIN	32.3 Gm.	VITAMIN B ₁	1.16 mg.
FAT	2.5 Gm.	RIBOFLAVIN	1.55 mg.
CARBOHYDRATE	66.3 Gm.	NIACIN	6.61 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
PHOSPHORUS	0.939 Gm.	VITAMIN D	400 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for skim milk.

The American Journal of **DIGESTIVE DISEASES**



An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

DIET IN UNCONTROLLED DIABETES PRECEDING ACUTE NEUROPATHY — <i>Howard F. Root, M.D. and Clovis Cruz Mascarenhas, M.D.</i>	173
FASTING BLOOD SUGAR VERSUS POST-PRANDIAL BLOOD SUGAR — <i>Anthony Sindoni, Jr., M.D.</i> ..	178
SUDDEN AND DRASTIC CHANGES OF THE CARBOHYDRATE TOLERANCE IN SEVERE INSULIN-TREATED DIABETES — <i>Arnold Galambos, M.D. and</i> <i>Wilhelmina Mittelman-Galambos, M.D.</i>	193
THE CONTROL OF DIARRHEA BY TOMATO POMACE — <i>Lester M. Morrison, M.D.</i>	196
EXPERIENCES IN NON-SPECIFIC DIARRHEAL CONDITIONS IN THE EUROPEAN THEATER OF OPERATIONS — <i>William J. Hanes, Major, M. C.</i>	199
EDITORIAL:	
HISTORY OF MEDICINE	210
ABSTRACTS OF CURRENT LITERATURE	211

Number 6

Company



ALL THE NUTRIENTS

Essential for a Food Supplement

Whenever the intake of essential nutrients must be augmented, as in convalescence from surgery or infectious disease, or in the correction of malnutrition, the delicious food drink which results from mixing Ovaltine with milk can be of significant value. This palatable food supplement provides a wealth of essential nutrients in a pleasant, easily assimilated form. It supplies protein of high biologic value, readily metabolized

carbohydrate, easily emulsified fat, ascorbic acid, B complex and other vitamins, as well as essential minerals. Three glassfuls daily sharply augments the intake of these nutrients, as shown by the table of composition. Its low curd tension makes for rapid gastric emptying, hence appetite for the next meal is not interfered with. This delicious food drink is enjoyed both as a mealtime beverage and between meals.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



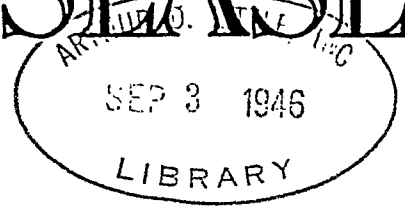
Ovaltine

Three servings daily of Ovaltine, each made of ½ oz. of Ovaltine and 8 oz. of whole milk*, provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B ₁	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	1.50 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.81 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
PHOSPHORUS	0.939 Gm.	VITAMIN D	417 I.U.
IRON	12.0 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

The American Journal of **DIGESTIVE DISEASES**



An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

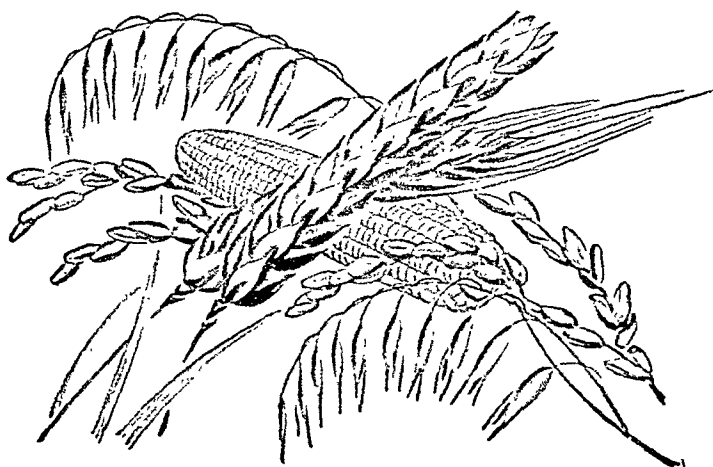
SOME EFFECTS OF GUM CHEWING ON GASTRIC ACIDITY IN HEALTHY INDIVIDUALS — <i>Clayton S. Smith, M.D., Helen L. Wikoff, Ph.D. and Martha E. Southard, B.A.</i>	245
TYROTHRIN IN PROCTOLOGY — <i>Alfred J. Cantor, M.D.</i>	247
RADIATION THERAPY OF THE CANCER OF THE ESOPHAGUS — <i>J. Borak, M.D.</i>	249
CONTINUOUS DRIP TREATMENT FOR CHRONIC ULCERATIVE COLITIS — <i>Juan Nasio, M.D.</i> ..	252
BRIEF PSYCHOTHERAPY IN THE TREATMENT OF GASTRO-INTESTINAL DISORDERS — <i>Malcolm L. Hayward, M.D.</i>	255
GASTRO-INTESTINAL SYMPTOMATOLOGY IN SCHIZOPHRENIA — <i>Jerome M. Schneck, M.D.</i>	257
PEPTIC ULCER. A ROENTGENOLOGICAL, LABORATORY, AND CLINICAL FOLLOW-UP OF 200 PEPTIC ULCERS — <i>A. J. Delario, M.D.</i>	260
EDITORIAL: PROCTOLOGY AND GASTROENTEROLOGY —	270
BOOK REVIEW: DIABETES — <i>Henry J. John, M.D.</i>	271
ABSTRACTS OF CURRENT LITERATURE	271

Volume 13

August, 1946

Number 8

Copyright 1946, The Sandfield Publishing Company



Meal Distribution and the Gastrointestinal Patient

The basic metabolic needs of the patient afflicted with gastrointestinal disease do not differ from the normal. Nevertheless many dietary problems do arise. Not only may the dietary have to be of a special nature, but meal distribution also may have to be adjusted. Frequent feedings or between-meal feedings, as required in peptic ulcer, gallbladder disease, and in colonic involvement, create problems in maintaining palatability and the patient's interest in food.

Cereals can play an important role in the dietary of the gastrointestinal patient. Whether ready to eat or to be cooked, they are easily digested with a minimum of effort. Except those made purposely different through the inclusion of bran, cereals leave virtually no residue on digestion, hence are bland and nonirritating to the intestinal tract.

The large number of cereals available makes for endless variety, hence

palate appeal is virtually assured.

Because of these nutritional advantages, cereals find excellent application not only in the formulation of breakfast, but as part of between-meal feedings and with the other two meals. The excellent nutritional contribution made by the cereal serving composed of 1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar is indicated by the table of composite averages:

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C
135 SOUTH LA SALLE STREET • CHICAGO 3

The American Journal of DIGESTIVE DISEASES

10/2

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

DIFFERENCES IN EXCRETION OF HIPPURIC ACID AND GLUCURONATES AFTER INGESTION OF SODIUM BENZOATE AND BENZOIC ACID — <i>I. Snapper, M.D., E. Greenspan, M.D. and A. Saltzman, M.D.</i>	275
ROENTGENOLOGICAL EVIDENCE OF APPENDICEAL ABSCESSSES — <i>Arthur Dallos, M.D.</i>	279
THE FASTING GASTRIC CONTENTS AS AN INDEX OF GASTRIC FUNCTIONING — <i>Frederick Hoelzel</i>	284
GASTROSCOPY AS AN AID TO DIAGNOSIS OF GASTRIC DISORDERS — <i>A. X. Rossien, M.D.</i>	290
OBSERVATIONS ON PERCUSSION OF THE LIVER IN ACUTE INFECTIOUS HEPATITIS — <i>Joseph I. Goodman, Major, M.C.</i>	294
IDIOPATHIC AND PSYCHOGENIC INCONTINENTIA RECTI — <i>A. Juda, M.D.</i> ..	296
THE CAUSES AND MECHANISMS OF ABDOMINAL PAIN — <i>Paul Jeffrey Schutz, M.D.</i>	299
BOOK REVIEWS:	
THE MODERN TREATMENT OF DIABETES MELLITUS — <i>William S. Collens, B.S., M.D. and Louis C. Boas, A.B., M.D.</i>	308
PEPTIC ULCER — <i>I. W. Held, M.D. and A. Allen Goldbloom, M.D.</i>	308
ABSTRACTS OF CURRENT LITERATURE	308



Acceptable

AT EVERY SEASON

Taken cold during the summer months or hot during the wintertime, the delicious food drink made by mixing Ovaltine with milk provides a wealth of essential nutrients in readily digested and assimilated form. Its delicious taste makes it enjoyable at every season. As a supplement to an inadequate diet, in the correction of the milder forms of malnutrition, or when the intake of all essential nutrients must be augmented, it makes a worth-while contribution, as

indicated by its composition shown in the table below. This dietary supplement provides biologically adequate protein, readily utilized carbohydrate, highly emulsified fat, ascorbic acid, B complex and other vitamins, and essential minerals. Its low curd tension makes for rapid gastric emptying and easy digestibility. It is relished by both children and adults, and is unusually acceptable either as a mealtime beverage or with between meal snacks.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL.



Ovaltine

Three servings daily of Ovaltine, each made of
 $\frac{1}{2}$ oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES	669	VITAMIN A	3000 I.U.
PROTEIN	32.1 Gm.	VITAMIN B ₁	1.16 mg.
FAT	31.5 Gm.	RIBOFLAVIN	1.50 mg.
CARBOHYDRATE	64.8 Gm.	NIACIN	6.61 mg.
CALCIUM	1.12 Gm.	VITAMIN C	39.6 mg.
PHOSPHORUS	0.939 Gm.	VITAMIN D	417 I.U.
IRON	120 mg.	COPPER	0.50 mg.

*Based on average reported values for milk.

The American Journal of **DIGESTIVE DISEASES**

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

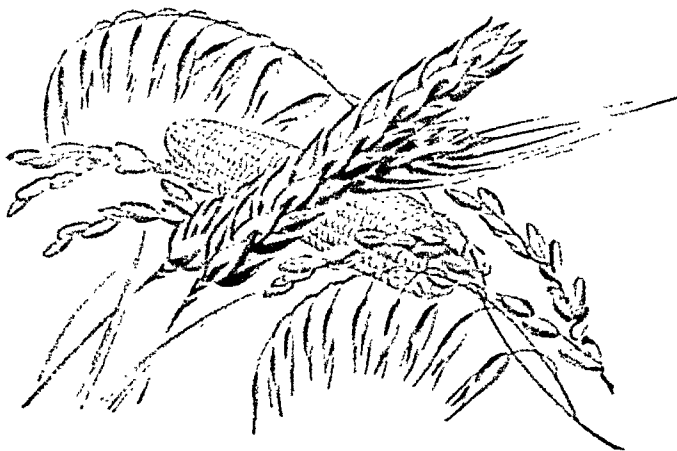
THE CONTROL OF MUSCLE SPASM AND ARTHRITIC PAIN THROUGH SYMPATHETIC BLOCK AT THE NASAL GANGLION AND THE USE OF THE ADENYLIC NUCLEOTIDE. CONTRIBUTIONS TO THE PHYSIOLOGY OF MUSCLE METABOLISM. PART II. — <i>Simon L. Ruskin, M.D.</i>	311
PHYSIOLOGICAL DERANGEMENTS IN ORGANIC DISEASE OF THE INTESTINAL TRACT — <i>Samuel Standard, M.D.</i>	320
PROCTALGIAS AND ALLIED NON-INFLAMMATORY PERIANAL DYSCRASIAS: COCCYODYNIA, PROCTALGIA FUGAX, NEUROGENIC PRURITUS ANI — <i>Emil Granet, M.D.</i>	330
PYROSIS. AN ANALYSIS OF ITS CLINICAL SIGNIFICANCE AND PATHOGENESIS — <i>G. W. H. Schepers</i>	333
EDITORIAL:	
DR. R. WALTER MILLS	338
BOOK REVIEW:	
SHOCK TREATMENTS AND OTHER SOMATIC PROCEDURES IN PSYCHIATRY — <i>Lothar B. Kalinowski and Paul H. Hoch</i>	339
ABSTRACTS OF CURRENT LITERATURE	340

Volume 13

October, 1946

Number 10

Copyright 1946, The Sandfield Publishing Company



The Importance of Breakfast In Restricted Diets

In the restricted dietary employed in the management of peptic ulcer, gall-bladder disease, colitis, or obesity, chief emphasis is placed on the chemical or mechanical properties of the foods chosen. Yet in the compilation of these diets, nutritional values are of equal importance, and must be taken into consideration in order to prevent development of subnutritional states.

From this standpoint, breakfast assumes added significance, since a good nutritional status can hardly be maintained without an adequate breakfast. Hence nutritionists assert that breakfast should provide from one-fourth to one-third of the daily nutrient and caloric needs. A widely recommended breakfast pattern to achieve this end consists of fruit, cereal with milk, bread or toast and butter, and a beverage. Through the addition of other suitable foods, a greater caloric and nutrient contribution is made possible.

The inclusion of the cereal serving

in this breakfast pattern is well founded. For the gastrointestinal patient, it provides a food which is mechanically and chemically bland, easily digested, and combines little bulk with excellent nutritional values. The serving of cereal, milk and sugar provides biologically adequate protein, caloric food energy in the form of carbohydrate and fat, B complex vitamins, as well as essential minerals. The quantitative contribution made by 1 ounce of cereal (whole grain, enriched, or restored to whole grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar is indicated by the table of composite averages:

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

The American Journal of **DIGESTIVE DISEASES**

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION ^{LIBRARY}

ORIGINAL CONTRIBUTIONS

INCREASED EXCRETION OF GLUCURONATES AFTER INGESTION OF BENZOIC ACID BY PATIENTS WITH DAMAGED LIVER — <i>I. Snapper, M.D., A. Saltzman, M.D., and E. Greenspan, M.D.</i>	341
HYPERTROPHIC GASTRITIS SIMULATING NEOPLASM — <i>Lt. Col. Joseph Bank, Major Alexander E. Pearce and Lt. Col. John H. Gilmore</i>	344
REGIONAL ENTERITIS AND IDIOPATHIC ULCERATIVE COLITIS. A CLINICAL STUDY — <i>B. J. Weinberg, M.D., H. Sorter, M.D., and H. Necheles, M.D., Ph.D.</i>	346
CLINICAL RESEARCH — <i>Horace W. Soper, M.D.</i>	350
REGIONAL ILEITIS. ISCHIO-RECTAL FISTULA PRECEDING AND FOLLOWING OPERATION FOR ILEITIS — <i>Meyer Golob, M.D.</i>	352
AMOEBIASIS: THE ROLE OF BACTERIA IN SYMPTOMATOLOGY — <i>Max Ellenberg, Lt.Col., M.C.</i>	356
BANTI'S SYNDROME FOLLOWING PROLONGED INFECTIOUS HEPATITIS. A REPORT OF TWO CASES — <i>Ralph Lee Fisher, M.D., and Morris Zukerman, M.D.</i>	361
THE PATHOGENESIS AND MECHANISM OF CIRRHOSIS OF THE LIVER — <i>Abraham O. Wilensky, M.D.</i>	367

Volume 13

November, 1946

Number 11

Copyright 1946, The Sandfield Publishing Company



As Appetite Declines WITH THE YEARS

The many somatic and emotional changes encountered in senescence are manifested in a variety of ways, especially by a decrease in appetite. Reduced energy expenditure, atrophic gastric changes, exaggerated food dislikes, and food intolerance all contribute, and not infrequently lead to a state of undernutrition. In older patients, this chain of events can easily produce excessive weakness and impaired stamina, adding to the burdens of senility.

Ovaltine proves an excellent means of preventing these complications. Its wealth of essential nutrients, as indicated by the table of composition, aids in preventing malnutrition. Made with milk as directed, Ovaltine is a delicious food drink. Older patients enjoy it as a mealtime and between-meal beverage, and especially as a bedtime drink. Its low curd tension assures easy digestibility and rapid gastric emptying, hence appetite is not impaired.

THE WANDER COMPANY, 360 N. MICHIGAN AVE., CHICAGO 1, ILL



Ovaltine

Three servings daily of Ovaltine, each made of
1/2 oz. of Ovaltine and 8 oz. of whole milk,* provide:

CALORIES.....	669	VITAMIN A.....	3000 I.U.
PROTEIN.....	32.1 Gm.	VITAMIN B ₁	1.16 mg.
FAT.....	31.5 Gm.	RIBOFLAVIN.....	2.00 mg.
CARBOHYDRATE.....	64.8 Gm.	NIACIN.....	6.81 mg.
CALCIUM.....	1.12 Gm.	VITAMIN C.....	39.6 mg.
PHOSPHORUS.....	0.939 Gm.	VITAMIN D.....	417 I.U.
IRON.....	12.0 mg.	COPPER.....	0.50 mg.

*Based on average reported values for milk.

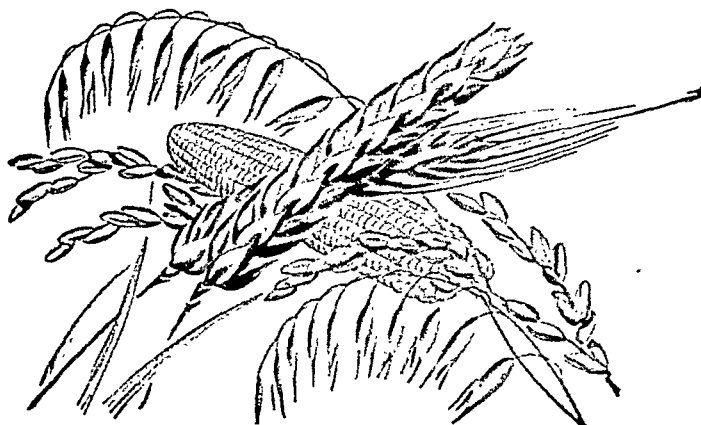
The American Journal of DIGESTIVE DISEASES

An Independent Publication
DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

TOXIC SULFONAMIDE COLITIS — <i>Harry Gauss, M. D., and L. J. Weinstein, M. D.</i>	373
SIMPLE NON-SPHINCTERIC LOCALIZED ESOPHAGEAL SPASM — <i>Morris Weiss, Lt. Col., M. C., AUS., and Leonard Long, Lt. Col., M. C., AUS.</i>	375
A MODIFICATION OF PLUMMER'S DILATOR FOR THE TREATMENT OF CARDIOSPASM — <i>Erling Lundsteen, M. D.</i>	377
CANCER OF THE STOMACH — <i>John A. Reed, A. B., M. D.</i>	379
EFFECTS OF POLYSACCHARIDES ON THE APPETITE AND EFFICIENCY OF FOOD UTILIZATION IN THE GROWING RAT — <i>B. H. Ershoff, Ph. D., and H. B. McWilliams, B. Sc.</i>	385
GASTRAGOGUE EFFECT OF LAXATIVES AND ALLYL-BROMIDE-MIXTURE — <i>Henry M. Feinblatt, M.D., and Edgar A. Ferguson, Jr.</i>	386
ANAL FISSURE — <i>David C. Ditmore, M. D.</i>	390
EDITORIAL:	
POSITIONING IN THE ROENTGENOLOGICAL EXAMINATION OF THE STOMACH	394
BOOK REVIEW:	
MANUAL OF APPLIED NUTRITION	395
ALLERGY (2ND EDITION) — <i>Ulrich Urbach, M. D., and Philip M. Gottlieb, M. D.</i> ..	395
MEDICAL BIOCHEMISTRY (2ND EDITION) — <i>Mark R. Everett, Ph. D.</i>	395
THE MANAGEMENT OF OBESITY — <i>Louis Pelner, M. D.</i>	395
DIABETIC CARE IN PICTURES — <i>Helen Rosenthal, B. S., Frances Stern, M. A. and Joseph Rosenthal, M. C.</i>	395
ABSTRACTS OF CURRENT LITERATURE	396
INDEX, YEAR 1946	XXXVII

ARTHUR D. LITTLE, INC.
JAN 7 1947



A Valuable Safeguard Against Ulcer Recurrence

After the acute exacerbation of peptic ulcer has been controlled, dietary measures are usually instituted to prevent recurrence of clinical activity and the characteristic discomfort. In the diet prescribed for this purpose, cereals enjoy a prominent position.

With the exception of those purposefully made different through the inclusion of bran, cereals are unusually bland, both chemically and mechanically. They invoke a minimum flow of acid gastric juice and do not impose a burden on the digestive processes. When served with cream, this cereal serving assumes greater acid inhibitory properties. These desirable features of cereals merit their use not only as part of the morning meal, but as a between meal feeding and as a component of the other two meals of the day.

The wide variety of ready-to-eat and to-be-cooked cereals available, and their characteristically different tastes and

physical properties, make for virtually endless variety and renewed taste appeal. Nutritionally, the average cereal serving makes a significant contribution, providing a mixture of proteins which is biologically adequate, readily available caloric food energy, B complex vitamins, and essential minerals. The table of composite averages outlines the nutritional contribution made by 1 ounce of cereal (whole grain, enriched, or restored to whole-grain values of thiamine, niacin, and iron), 4 ounces of milk, and 1 teaspoonful of sugar.

Calories.....	202
Protein.....	7.1 Gm.
Fat.....	5.0 Gm.
Carbohydrate.....	33 Gm.
Calcium.....	156 mg.
Phosphorus.....	206 mg.
Iron.....	1.6 mg.
Thiamine.....	0.17 mg.
Riboflavin.....	0.24 mg.
Niacin.....	1.4 mg.



The presence of this seal indicates that all nutritional statements in this advertisement have been found acceptable by the Council on Foods and Nutrition of the American Medical Association.

C E R E A L I N S T I T U T E , I N C .
135 SOUTH LA SALLE STREET • CHICAGO 3

Management of Chronic Constipation.

By

MICHAEL H. STREICHER, M. D.

CHICAGO, ILLINOIS

THIS entity entails primarily an intelligent understanding of the physiology of the colon before treatment is attempted. The physiologic principles which are so well established, yet so well forgotten, are suppression of the defecation reflex, the lack of fluid intake, intake of too much or too little residue in the diet, undue physical or mental strain, lack of adequate exercise, and in general, lack of proper understanding and evaluation of associated conditions.

A routine pattern of treatment unfortunately does not apply in constipation. It is well in general to study each patient as a unit and to apply the physiological principles in individual instances, inasmuch as patients vary considerably in their daily life and work. Specifically, it is essential to obey the call of the defecation reflex, so well described by Hurst (1921), and to that end it is important to teach each patient to think about it each morning after breakfast. It is equally important that he concentrates on the process and avoids undue distractions. Suppression of this reflex (habit) often leads to atony of the musculature (dyschezia).

In general, the average requirement of fluid intake is 1500 to 1800 c.c. per day. Bearing in mind that absorption of fluid takes place primarily in the right half of the colon and that absorption is more rapid in some patients, one must strive to estimate a daily requirement in each case; for instance, a constipate, who in addition has a decompensated heart disease, will necessarily need less fluid intake than one who is badly dehydrated.

The problem of intake of residue while well understood by many, is misguided in its application. In a young individual, one who presumably has active musculature of the colon and is lacking in a substantial amount of cellulose in the stool (measured by weight in 24 hours)* or by direct observation, it is helpful to increase the residue in the diet, but it is detrimental to prescribe a high residue diet for one who has an atonic bowel or a depressed activity of the neuromuscular mechanism of the colon as in senility.

Constipation which is produced by a spasm of any portion of the colon (Spastic constipation) may be considered as a tonic state of the musculature of the colon and may be brought about reflexly by diseases within the confines of the abdomen as well as by influences controlled centrally. Much comfort has been afforded to this group by the use of atropine in reducing the tonicity of the parasympathetic nerve endings of the colon; the mere fact that these patients become addicted to atropine is in itself sufficient proof of its

failure. One must approach this group at its foundation. Constipates should be studied diligently and once the precise etiological factor is established, therapy may be instituted accordingly.

Atonic constipation is a group in which the musculature of the colon, the pelvic floor, the diaphragm and the abdomen is weakened or depressed in activity; the causative factors include debilitating disease of organic nature, as lesions of the central nervous system, nutritional deficiency disease in which the diet is low in vitamin B or calcium or potassium, and many metabolic processes as obesity, senility, and a group deficient in endocrine gland secretion.

Production of constipation is also ascribed to mechanical causes such as post-operative adhesions, tumors (extracolonic) and to undue anatomic angulation of the recto-sigmoid junction; mechanical obstruction due to sharp angulation of the pelvic colon is familiar to us inasmuch as we made a survey of this particular type proctoscopically on a large group of patients. It is obvious that many of these cases of severe constipation produced by mechanical obstruction must be treated surgically, while the type brought about by acute angulation of the colon can be managed successfully by a low residue diet supplemented by essential vitamin requirements and lubrication of the intestinal canal, if necessary.

One of the essentials in the management of constipation is the recognition of the fact that all patients in this group have been self-treated, that most of them have taken enemas or too much medication and many take medicines at wrong hours; it is therefore best at the onset to discontinue all previous programs and to start anew along the following outline:

1. Establish and correct the physiology in each patient over a 24-hour period.

2. Outline a diet in keeping with basal requirements and supplement essentials needed in amount of residue and vitamins. The work of Cowgill (1933) suggests that for adequate laxation the physiologic fiber minimum in a diet should be 100 mg. daily. Cowgill studies were made with the use of wheat bran as a laxative. Extensive studies were made by Streicher and Quirk (1940) and (1943) on the evaluation of bran as a laxative. Our conclusion was that bran administered orally aids bowel activity.

3. If the simple procedures do not correct the condition it becomes necessary to resort to medications; it may mean that laxatives may be utilized only temporarily but the extreme chronic obstipation may commit one to a habitual use of a minimum requirement. The choice of the laxative, the amount used, and the hour of intake is paramount.

Grant Hospital.

*Average weight of stool in 24 hours is 100 grams.

stipation, bowel movements seldom and by enema only, abdominal distention, visible peristalsis, muscle atrophy of the abdominal wall, toxic symptoms, X-Ray findings of megacolon after barium by oral application or by enema.

One interesting, but evidently only rarely occurring syndrome may be mentioned because at least one author refers to it in connection with congenital megacolon: Etzel describes the presence of mega-esophagus, megacolon, and mega-ureter and asks whether this disease complex may be caused by chronic Vitamin B₁ deficiency. This Vitamin B₁ deficiency is thought to be the etiologic agent responsible for the degeneration in the autonomic nervous system. It is not clear whether this Vitamin B₁ deficiency is supposed to act upon the pregnant mother thus causing the disease complex in the new born baby.

The usual absence of vomiting and abdominal pain, at least as long as no acute peritonitic complication is present, is especially dangerous because the layman waits for such an alarming signal. This is the reason why cases of fully developed megacolon even nowadays are presented to the physician late. The parents feel at ease since the infant does not vomit and evidently has no pains. Whereas dyspnea resulting from restriction of the diaphragmatic movements due to increased intra-abdominal pressure is most alarming to the parents. Sometimes one sees peristaltic waves moving across the abdomen, its presence depending upon the degree of involvement of the large intestine due to partial atony of the colon (partial megacolon). In such a case, the differential diagnostic problem of mechanical intestinal obstruction or megacolon comes up. History, absence of bowel movements since early infancy may facilitate the diagnosis. The decision whether immediate surgery is indicated to relieve an intestinal obstruction, or conservative treatment should be applied, may be difficult. X-ray examination with or without barium enema may help in establishing the diagnosis. In cases of acute intestinal obstruction a flat plate may show the air and fluid levels, whereas in Hirschsprung's disease already a small amount of barium, given by enema, may show the dilatation of the colon. As in most cases of abdominal surgery in childhood, the decision is difficult. The physician has to establish the diagnosis and should not forget that intestinal obstruction is more frequent than Hirschsprung's disease and has to be dealt with by surgery immediately. All cases of congenital megacolon complicated by ulceration or necrosis of the intestinal wall plus peritonitis or perforation into the open abdominal cavity also require fast diagnosis and immediate transfer to surgery. The danger resulting from ulceration and perforation in a case of congenital megacolon is enormous: the colon is loaded with gas and feces, the bowel wall may be thin, almost transparent, its rupture imminent. Due to inflammation from impacted feces and necrosis of the mucosa, involvement (hypertrophy) of the mesenteric glands develops. Thrombosis of the mesenteric vessels and volvulus of loops loaded with feces make an acute exacerbation in a case of advanced

and neglected megacolon one of the toughest problems in infant surgery with poorest prognosis.

Since megacolon has first been described and defined under the name of Hirschsprung's disease as a congenital and not acquired condition, the search for an explanation and for a cure has not ceased. One theory explains congenital megacolon as a partial gigantism on the basis of a neurogenic dystrophy. The long line of therapeutic methods finally led to the conclusion that congenital megacolon and its clinical manifestations are the result of a primary sympathetic-parasympathetic unbalance, with marked underactivity of the parasympathetic innervation of the colon (Griffith and Mitchell). The beneficial results following, usually the interruption of the sympathetic impulses to the colon by chemical and surgical means seem to strengthen this theory. Some fatal cases of newborn infants showing both dilatation of the colon and hypertrophy of its muscularis were described. It is the question whether there is primarily a failure of the rectosigmoidal apparatus to relax or whether there is a failure of the motor function of the parasympathetic system to act effectively above the rectosigmoidal region. This question seems to be solved in the latter direction. A great number of publications stress the beneficial effect of interruption of the sympathetic impulses to the colon by chemical and (or) surgical procedures. They seem to clarify the picture in favor of the above mentioned primary sympathetic-parasympathetic unbalance with underactivity of the parasympathetic innervation of the colon. They speak against a primary failure of the rectosigmoidal apparatus to relax. The inability to relax may be explained as a secondary "nervous" irritability of this rectosigmoidal region, an observation made occasionally as a complication to some other pathology of the colon.

Needless to say that also in Hirschsprung's disease we find abortive cases, patients with slight dilatation and minor symptoms, with rare evacuations, but without the severe disturbances of general health. These frustrated cases of congenital megacolon may become evident only later in life. Some authors put the age limit of this congenital megacolon at 20 years and thereby are willing to call these late cases still in forms of Hirschsprung's disease. Thorough investigations of these cases mostly reveal that the patient suffered from severe constipation since early childhood. But in these cases of late manifestation one should look with all diagnostic means (rectal examination, proctoscopy, X-ray with barium enema, a. s. o.) for some acquired obstacle in the lower parts of the colon. In these patients of the older age group a primary congenital or acquired mechanical obstacle is most probable. There was, at least sometimes, doubt whether the megacolon is really congenital, present at birth. The congenital occurrence is also proved by the inheritance of megacolon congenitum in some families, and by the proven fact that the same condition was found in five members of one family (Richard and Eduard Muehsam). Although the presence of several cases of Hirschsprung's disease in one family is certainly

exception, its proven fact without doubt supports the congenital nature of Hirschsprung's disease.

Various etiologic factors were advanced for this congenital nature of Hirschsprung's disease: Congenital hypoplasia of the muscularis of the lower colon, hypoplasia of the elastic elements of the intestinal wall, and finally the modern concept of congenital disturbance of innervation. Increased tonus of the sympathetic and



HIRSCHSPRUNG'S DISEASE

(or) diminished tonus of the vagus are blamed for the congenital nature. Nervous dysfunction of the central innervation (and not of the distal muscular tonus) is blamed for causing the disturbance. The trophic tonus towards the nerve is out of order. In one of the first publications of this "neurogen" theory Bruening looks at congenital megacolon as a partial gigantism, due to lack of inhibiting trophic nerves and a disturbed formation of the segmental sympathetic centers. This theory explains the fact that in most cases the border between enlarged and normal colon is at the end of the sigmoid and beginning of the rectum, the latter being involved only rarely. The explanation is that the rectum has another innervation than the higher parts of the colon, its centers lying in lower parts of the spinal cord. The few cases with involvement of the rectum may be explained as congenital dilatation of the higher parts of the colon complicated by secondary dilatation of the rectum due to sphincter spasm (from impacted fecal masses *e. g.*).

Whatever theory we may accept—and the "nervous" concept seems to be the recognized one — there is no doubt that the post-natal development of a case of megacolon depends largely upon secondary conditions. The various features to which a congenitally wide colon is exposed, are considerably influenced by secondary circumstances. The large colon is in permanent danger of congestion and accumulation of gas and feces, the wide loops of intestine with an elongated mesocolon being predisposed to incomplete or complete ileus. Presence of gas producing bacteria augments this risk. The change from breast to artificial feeding seems to be an especially dangerous period. The heavy loops of intestine tend to knee formations, thereby causing adhesions as well as valve and pseudo-sphincter formation, often found in congenital megacolon. Frequently normal folds in the intestinal wall are the sites of these mechanical obstacles. Here we may find later on the ulcers, necrosis and perforation, the dense adhesions of the outer intestinal layers causing acute complications (intestinal obstruction, peritonitis, *a. s. o.*). These folds are often responsible for the development of an obstruction; thus in some cases an acute condition of distention can be overcome at least temporarily by a rectal or long intestinal tube in combination with a high colonic enema or lavage. The tube or the water running up into the intestine opens the folds or valves in one direction, thereby emptying the accumulated gases and feces and relieving for some time the acute emergency. This is no cure but a way to avoid an emergency operation under great risk for the debilitated infant. The patient then can be prepared for one of the modern treatments of Hirschsprung's disease at a time chosen by the physician. This palliative treatment of emptying the intestine, repeated if necessary, may prevent congestion of the colon, hypertrophy of its muscular parts, elongation of the heavy wide loops, and destruction of the various layers of the intestinal wall. Ulcers and necrosis of the mucosa originate from stretching of the wall and pressure of fecal tumors against its mucosa. This palliative emptying of the bowels may further on obviate intoxication and inanition as well as disturbances of lungs and heart due to increased intra-abdominal pressure. Anuria with subsequent uremia may occur from compression of ureters or urinary bladder by the powerful intestines. This severe complication, too, may be relieved temporarily by rectal tubing or lavage. The beneficial and instantaneous relief of emptying the bowels from accumulated gas and feces decreases the otherwise considerable circumference of the abdomen, the layers of which are thin and show a complete atrophy of the muscles of the anterior abdominal wall. Thus, fecal tumors or adherent intestinal loops can be felt or even seen through this paper thin abdominal wall.

The newborn infant may show no signs or symptoms at all. Although the absence of meconium should warn parents and physician. The slowly increasing abdomen may be alarming, but, unfortunately, often only the last and sometimes irreparable damage to general health induces the parents to call for the doctor.

The diagnosis, in early cases, may be suspected from the child's history and should be verified by X-ray both from above and below. Differential diagnostic problems may come up from a tumor of any intra- or extra-abdominal organ (liver, spleen, glands, kidney, a.s.o.). But intestinal obstruction from any other condition and the important and more frequent intestinal intussusception should be taken under serious consideration, this latter condition being a frequent complication of congenital megacolon. In a case of advanced Hirschsprung's disease, the heavy intestine may fall due to its weight into the lower loops and simulate a true invagination (intussusception). If neglected or overlooked, congenital megacolon is bound to develop towards the secondary disturbances and interference with general health (compression of the stomach causing inanition

place for one or two days may be used for irrigation of the rectum and lower colon several times daily. Drugs may be helpful in depressing or paralyzing the parasympathetic nerve endings in the intestine: Atropine or the parasympathetic paralyzant syntropan which produces fewer unpleasant secondary effects, and other spasmolytic drugs are recommended. Prostigmine or similar drugs increasing peristalsis by the way of stimulating the parasympathetics are used when the parasympathetic impulses are too weak to initiate the expulsive mechanism of the colon (Griffith and Mitchell, et al.). Reeves and Harrison mention treatment of hypotonic megacolon by administration of pancreatic tissue extract. Sheldon, Kern, Hakanisson report that constipation due to idiopathic dilatation of the colon is relieved by parathormone. A hugely dilated colon was reduced to normal size in eight days! There may be a relation of abnormal parathyroid function to disorders

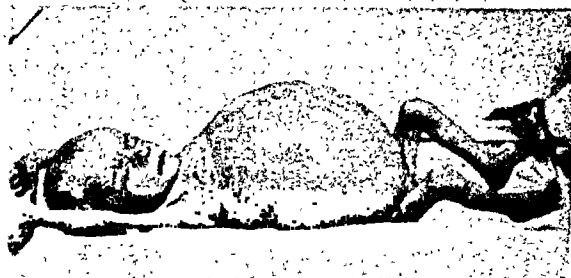


HIRSCHSPRUNG'S DISEASE IN A SIX WEEK OLD INFANT

and emaciation from inability of intake of food, failure of lung and heart function, even severe edema due to interference with both heart and kidney action).

As soon as the diagnosis of congenital megacolon has been established treatment should start. It is widely dependent on the extent of the disease at the given moment. Long standing constipation should first be treated with the well-known methods. Second stage cases with high-grade accumulation of gas and feces and with visible or palpable tumors of impacted feces have to be considered with the view to more radical procedures after preparing the patient for neuro- or abdominal surgery. The third and often desperate phase of acute intestinal obstruction, extreme emaciation, with or without exact diagnosis, may require surgery as a purely palliative method.

The conservative treatment of congenital idiopathic megacolon should try to improve general health and prevent it from further getting deteriorated. Prophylaxis as well as general care and hygiene are important. Emptying of the bowels and avoiding overdistention are essential (enema, high colonic lavage). Friedell treats congenital megacolon by daily hot irrigations of normal saline solution at 115 degrees, and reports good results. Light massage of the abdominal muscles may support evacuation of the bowels. A soft rubber tube of medium size inserted into the sigmoid and left in



HIRSCHSPRUNG'S DISEASE

of intestinal motility and to megacolon. But there is a danger from prolonged parathormone administration. These are only a few of the drugs recommended to stimulate the parasympathetic and to produce normal rhythm of the intestines, i. e. peristalsis. The multitude of symptoms in congenital megacolon, the different forms of appearance due to greater hypotony of the walls or thickening of the intestinal layers as a secondary hypertrophy explain the lack of any single therapeutic approach to this complex condition.

If the treatment starts at a time of considerable distention, the paramount problem is how to dispose of the gases. Intra-intestinal catheterization by the Wangenstein or by the Miller-Abbott technique are of great value. These methods are not applicable to or successful with all patients. The question of a laxative is a problem in itself as in many border cases of the abdominal type. If the condition is already complicated by peritonitic involvement the laxative may be harmful. Increased peristalsis produced by a laxative or a drug may cause an abdominal catastrophe from an ulcerated intestinal wall. Mild laxatives mostly are without results. Some laxatives — such as Calomel — should never be given when the elimination is not guaranteed since the danger of poisoning is imminent. Castor oil, one of the best laxatives, may give good results in obstinate constipation, especially if simul-

taneously the bowels have been emptied mechanically by high enema or colonic lavage. But the danger of castor oil (as often) lies in its possibly strong effect upon the peristalsis. Increased intestinal movements may complete an imminent perforation. Therefore, in trying to relieve constipation in congenital megacolon only mild laxatives (mineral oil, milk of magnesia, a.s.o.) should be tried and if necessary given repeatedly over a long period of time. There certainly are cases which are absolutely refractory and are not influenced by any means. These should be emptied manually. All these procedures as well as simple enemas and high colonic lavages are not harmless. The instillation of considerable amounts of water under a certain pressure may mechanically break up adhesions or the thin layers covering ulcers and necrosis of the wall thus producing a perforation of the intestinal contents into the abdominal cavity. There may however be a small chance of improving initial cases with chronic constipation and slight dilatation. As long as cases of Hirschsprung's disease have not yet developed the full picture of secondary complications, these conservative measures are worthwhile trying.

Of great importance in treating Hirschsprung's disease and preventing further damage is the diet. All food increasing constipation should be avoided. Breast feeding should be continued as long as possible since the change from breast to artificial feeding is a dangerous period. This is a great problem for the pediatrician. At least 70 per cent of the cases show symptoms in the first few weeks of life. Some of these infants may respond to immediate intensive conservative treatment, daily irrigations, rectal dilatation, to overcome a secondary sphincter spasm, and parasympathetic drugs.

A new approach has been offered in the way of medical treatment by introducing acetyl-beta-methylcholine-bromide. This drug has been administered with promising results to children with congenital megacolon (Law, Goodman and Gilman). It was first used to test the functional ability of the musculature of the colon prior to surgical intervention, and has since been accepted as one of the best and most promising medical treatments. Acetyl-beta-methylcholine-bromide in moderate doses causes an increase in tonus, contraction and peristalsis of all parts of the gastro-intestinal tract. It is a "parasympathetic activator" (Barenberg, Greene and Greenspan). It may even be that after sympathectomy the acetyl-beta-methylcholine-bromide supplements the effect of the sympathectomy, and thus both (neuro-surgery and parasympathetic activator) together improve the condition. Whereas atropine as a spasmolytic counteracts the motor gastro-intestinal effects of acetyl-beta-methylcholine-bromide, the small and large intestines are stimulated by average oral and subcutaneous doses of acetyl-beta-methylcholine-bromide. It may cause increased peristalsis, increased bowel movements and more frequent defecation. But, as most drugs, even acetyl-beta-methylcholine-bromide may turn out to be two-edged. The danger of bromide poisoning is involved in cases of bromide intolerance. Law, in comparing the results of symp-

thectomy with the effect of acetyl-beta-methylcholine-bromide, comes to the result that the influence of the drug is as good as neuro-surgery and less dangerous. There may be cases, where drug therapy and neuro-surgery should be combined. Sympathectomy has not solved the therapeutic problem. Neuro-surgery does not immediately restore the normal functional activity of the bowel, since megacolon congenitum is probably caused by functional unbalance of the autonomic nerve supply to the colon. Therefore it is usually necessary after the operation to stimulate the peristalsis by enemas, laxatives, and the acetyl-beta-methylcholine-bromide. The latter is, as Law calls it, "the remedial agent for diminished tonus of the parasympathetic nerves." An interesting conclusion leads several authors (Fine, Starr, Banks, Hermanson, Frehling) to another conservative treatment. They recommend the absorption of air from the body tissues and cavities by



MEGACOLON AFTER AUTOPSY

inhalation of ninety-five per cent oxygen. Inhalation of high concentrations of oxygen (95%) facilitates the absorption of the nitrogen from the gut by preventing the inhalation of nitrogen into the inspired air, thus causing its diffusion out of the blood and desaturating the tissues and body cavities of their nitrogen. A considerable shrinkage of abdominal girth can be observed along with substantial subjective relief to the patient. Its value in distention accompanying pneumonia or cardiac diseases or other cases of overdistended, but unobstructed, intestine has been proved by Fine and Starr. When properly used, the dangers of oxygen poisoning can be avoided (Fine, Banks, Hermanson). If the distention is due to established mechanical obstruction, surgery is the method of choice. But inhalation of 95% oxygen may be used even here to advantage before or after the laparotomy (Fine, Hermanson, Frehling). It seems to me that this method of inhalation of 95% oxygen should be tried in cases of congenital megacolon, even when emergency surgery is indicated, in order to decompress the gut. Every method of emptying the colon from its dangerous and highly infectious content before the operation should be applied.

The number of conservative methods to be tried in Hirschsprung's disease is great. In cases of neuro-

genic unbalance due to faulty inhibitory or motor function of the parasympathetic system, selective drug therapy has proved effective. Change of environment by placing patients under hospital routine and diet is stressed by some authors (Klingman et al.) as a valuable supporting measure. It is difficult to state how long medical management may be continued without endangering the patient and missing the right time for surgery. As soon as an emergency arises and immediate surgery has to be performed, the chances for recovery diminish rapidly. Prophylactic surgery nowadays does not consist in the abdominal approach but in neuro-surgery. Radical abdominal surgery as a cure, at the moment chosen by pediatrician and surgeon, should be performed only after neuro-surgery has been done. If neuro-surgery has been performed, then only radical surgery (one-stage resection plus ileosigmoid-enteroanastomosis) should be considered. Then the resection is the operation of choice (Richard and Eduard Muehsam; Grimson, Vandegrift and Dratz, Duke University, School of Medicine). Colostomy is an emergency operation to be performed only under critical conditions. Radical resection is the last and curative procedure. Medical treatment involves high mortality. Thorough history, proctoscopy, roentgen examination from above and below should determine the best possible time for neuro-surgery.

There was no satisfactory treatment in surgery before 1926 when Wade introduced his operation, the left lumbar sympathetic ramisection. It should not be forgotten that sympathectomy decreases or interrupts the impulses over the sensory pathways for visceral pains. These visceral pains give early warning of impaction, pressure necrosis, volvulus or perforation. These alarming signals, well known to and appreciated by the physician can not be relied upon any more after sympathectomy. Their loss means a certain danger after sympathectomy. Therefore, after sympathectomy or any other form of neuro-surgery, medical management and supervision should never be discontinued. Sympathectomy does not greatly change the gross pathology.

A good test for sympathectomy seems to be a trial application of spinal anesthesia. By giving sufficient spinal anesthesia to paralyze the anterior nerve roots up to and including the sixth dorsal segment, if necessary repeated after ten days, in suitable cases normal bowel movement may set in and hold on for a considerable length of time. Spinal anesthesia is regarded as a therapeutic test as to whether sympathectomy will be effective. A similar therapeutic test is the paravertebral procaine block or lumbar infiltration. This therapeutic test selects the cases to be subjected to neuro-surgery after all medical management has been tried. The left lumbar sympathectomy consists in the removal of the presacral nerve and its lateral roots, the intermesenteric plexus and whatever ganglionic masses are found on the inferior mesenteric artery (Barenberg, Greene, Greenspan). It is a lumbar sympathectomy and ganglionectomy done from a retroperitoneal approach. Another access for neuro-surgery

is the division of the lower lumbar sympathetics plus presacral nerve by laparotomy. Bilateral lumbar sympathectomy is excision of superior hypogastric plexus with presacral nerve and a combination of lumbar ganglionectomy with section of splanchnicus. This bilateral method is more extensive. Sterility in males may result from bilateral procedure. Since males are more often affected than females (in a ratio 3 or 4 to 1), one should always be conscious of the danger of sterility resulting from bilateral lumbar sympathectomy. Radical, i.e. bilateral sympathectomy therefore should be applied only in such cases in which left lumbar sympathectomy has shown incomplete but encouraging result. For intractable cases after the age of three years sympathectomy is recommended. Interruption of the sympathetic pathway to the colon by lumbar sympathetic ganglionectomy or ramisection has led to beneficial results, especially when the distal portion of the colon is greatly involved. But sympathectomy may prove insufficient. It is never a cure. It has to be followed, if ineffective or if radical cure should be attempted by resection of the colon (DeTakats and Biggs).

Surgery in idiopathic dilatation of the colon can be divided in emergency operations and those operations performed at the time and place chosen by the surgeon. If all medical-conservative as well as neuro-surgical measures have failed or proved to be insufficient, abdominal surgery should be taken into serious consideration. The number of procedures for abdominal surgery is great. The oldest way to relieve the overdistended colon — now abandoned — shall be mentioned only for historical reasons and completeness of enumeration: Tapping of the colon. It should not be done anymore. It helps, if at all, only for a very short time and is highly dangerous. Cecal fistule (artificial anus), colotomy, colostomy, cecostomy are emergency operations to be performed only in cases of acute intestinal obstruction, volvulus, intussusception, perforation and peritonitis. The old method of appendicostomy is also generally abandoned. More conservative methods are colopexy, shortening of mesocolon, fixation and suspension of the colon at the parietal peritoneum, and enteroanastomosis. They give poor results only and do not fulfil the paramount aim in surgical treatment of Hirschsprung's disease: They do not reduce the too large colon and its too large absorbing surface, and do not diminish or stop the resulting fecal poisoning. The modern surgery asks for resection of the entire diseased colon. It is a radical method. Simple anastomosis between the ileum and the lowest part of the colon without resection of the colon gives no hope for relief from and improvement of obstipation. The condition may even become worse, since the fecal stream may not be directed into the anastomosis. It may enter the colon, increasing accumulation of gas and feces in the colon. Since the lower sigmoid is mostly normal, the anastomosis after removal of the entire diseased colon should be an ileo-sigmoid-anastomosis. The technical procedure in performing the radical colon resection plus ileo-sigmoid-anastomosis may be multiform.

One-, two-, and even three-stage resection is recommended. The decision depends highly upon the condition of the intestinal wall. There may be changes in the distended and over-extended wall which advise against primary reunion of the intestinal openings. These cases may require a two-, or even a three-stage operation. As a general rule, we may say: The more acute the case, the more subdivided the procedure should be. In uncomplicated chronic cases without any acute signs or symptoms of over-distention, ileus or damage to the intestinal wall, the radical one-stage resection of the entire colon plus ileo-sigmoid-anastomosis is the operation of choice to heal the congenital

Photos taken from Richard and Eduard Muehsam, Hirschsprungsche Krankheit, Neue Deutsche Klinik, Vol. 5, 1930, p. 110.

megacolon.

This description of the complex condition of congenital megacolon or Hirschsprung's disease from its first publications before and by Hirschsprung until today shows a cross-section through medicine. It reaches from the old times of simple medical experience and medical intuition to the modern times of highly trained physicians working with the help of modern equipment and modern medical concept. The improvement reached in the case of Hirschsprung's disease shows clearly how far medicine has advanced during the last century. These good results in treatment of congenital megacolon could be achieved only by the close cooperation of all medical specialties.

REFERENCES

- Barenberg, Greene, Greenspan: *The Journal of Pediatrics*, Vol. 18, 1941, p. 579.
Brœnnemann's *Practice of Pediatrics*, 1945, Vol. 3, Chapter 7, p. 10.
Bruening: 49. Tagung der Deutschen Gesellschaft fuer Chirurgie, 1925.
Court and Halser: ref. *Amer. Jour. Dis. of Chil.*, Vol. 66, 1943, p. 674.
De Takats and Biggs: *Jour. Pediat.*, Vol. 13, 1938, p. 819.
Etzel: *Amer. Jour. Med. Sc.*, Vol. 203, 1942, p. 87.
Fine, Banks and Hermanson: *Ann. Surg.*, Vol. 103, 1936, p. 375.
Fine, Hermanson and Frehling: *Ann. Surg.*, Vol. 107, 1938, p. 1.
Fine and Starr: *Rev. of Gastroenter.*, Vol. 6, 1939, p. 419.
Friedell: *Minn. Med.*, Vol. 21, 1938, p. 175.
Goodman and Gilman: *The Pharmacological Basis of Therapeutics*, 1941, p. 366.
Griffith and Mitchell: *Textbook of Pediatrics*, 1941, p. 506.

- Grimson, Vandegrift, Dratz: *Amer. Jour. Dis. of Chil.*, Vol. 68, 1944, p. 102.
Hawkins, Brennenman's *Practice of Pediatrics*, 1945, Vol. 3, Chap. 7.
Hawksley: ref. *Amer. Jour. Dis. Chil.*, Vol. 68, 1944, p. 146.
Hindmarsh: ref. *Amer. Jour. Dis. Chil.*, Vol. 65, 1943, p. 820.
Hirschsprung, *Jahrbuch fuer Kinderheilkunde*, Vol. 27, 1888, p. 1.
Klingman: *Jour. Pediat.*, Vol. 13, 1938, p. 805.
Law: *Amer. Jour. Dis. Chil.*, Vol. 60, 1940, p. 262.
Law: ref. *Jour. Pediat.*, Vol. 13, 1938, p. 940.
Muehsam, Richard and Eduard: *Neue Deutsche Klinik*, Vol. 5, 1930, p. 110.
Penick Jr.: *J. A. M. A.*, Vol. 128, 1945, p. 423.
Reeves and Harrison: *Radiology*, Vol. 28, 1937, p. 731.
Sheldon, Kern, Hakanson: *Amer. Jour. Med. Sc.*, Vol. 184, 1932, p. 94.
Whitaker: *Rev. of Gastroent.*, Vol. 1, 1934, p. 270.

Some Dermatologic Aspects of Allergy

By

JOHN A. TURNBULL, M.D.

BOSTON, MASS.

SKIN diseases, whether limited to the skin itself or merely manifestations of some more generalized condition, may be divided, with regard to their symptoms, into objective and subjective groups. Objective symptoms comprise elementary lesions of the skin, which may again be subdivided, as primary and secondary. Subjective symptoms, which may or may not be present, and in any degree of intensity, include such indications as pain, tenderness, heat, tingling, itching, smarting and the like. These are usually associated with inflammatory conditions.

Again, skin disease may be the primary event, with more general disturbances secondary to it; or it may be secondary to some systemic disturbance in the alimentary canal, the genito-urinary system or elsewhere. Extensive skin disease may lead to fever or other individual symptoms, or to general vital depression. Conversely, systemic conditions may result, indirectly, in surface disorders.

Heredity also plays an important part in the production of disease, though the child may not inherit literally the same condition as that suffered by the parent, or parents, but rather some related affection.

For all these reasons, it is extremely important that every possible factor be weighed, when attempting to diagnose any departure from health.

The question as to the cause or causes of the current outbreak, can only be answered satisfactorily by the physician, after eliciting from the patient, both by questions and by physical examination, all the conditions, both external and internal, that led up to it. Such questions and examination may or may not give a clue to the real source of the trouble; without the assistance of a knowledge of allergy, many cases remain a good deal of a mystery.

However, right here let me sound a warning — this work can only be done to the best advantage by a physician well trained and widely experienced in this branch of medical study — as is interestingly demonstrated in cases *iii* and *vi* below. Such training and experience must include testing with many types of allergens, — foods, pollens, plant life, clothing, animal emanations, medicines and other chemicals, cosmetics, and many others — any one or several of which may affect the particular case under consideration. The physician must also be well versed in dietetics, because

of the importance of diet in the treatment of any person afflicted with an individual allergic sensitization.

In the following series of cases, examples of a number of diverse conditions will be found. With these dermatological disturbances, these patients usually showed also, some systemic condition, resulting from dysfunction of one or more of the internal organs. The systems affected include cerebral, aural, oral, visual, nasal, pharyngeal, laryngeal, respiratory, gastro-intestinal and articular. Some of the cutaneous conditions were preceded, by periods of months or years, by other lesions resulting from different allergies.

In presenting these cases, it is my purpose to show how important a part may be played by allergies in any of the conditions cited. I have purposely included so large a number of examples in order to demonstrate that relief through direct treatment for the allergy, was no mere accident—a conclusion which might be drawn by some from a smaller series. Of particular importance is the fact that not only were the cutaneous conditions cleared up by treatment of the allergies, but the systemic affections as well, a result worthy of the most serious consideration.

ECZEMA.

This condition serves as an excellent example of an inflammation beginning in the papillary layer of the skin, and later extending—when of sufficient duration—to the entire structure, both above and below. Vasomotor disturbances of the cutaneous and subcutaneous layers also occur about the affected area. While the entire skin structure is often involved from the onset, one may find that different layers take a predominant part. However, the longer the process endures, the more surely will the entire structure be affected.

When there is marked inflammation, vaso-paresis takes place, with extravasation—serum, blood, blood coloring matter—into the skin. This, in turn, gives rise to vesicles when the upper layers of the epidermis are elevated by fluid forced up from below because of either mechanical or inflammatory pressure. The contents of these vesicles may be clear, turbid or blood-stained.

CASE I

Female, aged 5. Eczema since age 3 months, asthma since age 9 months. Both steadily increased since onset. Eczema covering entire body, equally inflamed throughout. Increased difficulty in breathing at frequent intervals. Abdomen greatly distended. History shows that when horses were near patient's home, asthma at once became very severe, with marked increase in eczema within a few hours. Beef or eggs cooked in house, same effect. It is interesting to note that though this child showed no ill effects from eating pork when it was kept separate from food of rest of family—as was done with all food—severe reactions appeared within 4 hours after eating roast pork which had merely been kept in same refrigerator with roast beef.

Cutaneous tests showed sensitivity to horse, beef, egg, silk and some other substances. Diet and suitable precautions prescribed. In 2 weeks, 50% decrease in eczema, 70% in asthma. Distention of abdomen completely re-

lieved. Within 4 weeks, there was complete recovery from both asthma and eczema.

One year after original visit, child was brought in again for check-up. Though she had been free from symptoms the entire year, when she arrived at my office, some 30 minutes after leaving home, she was having severe asthma and scratching with both hands. Upon investigation, I found she was wearing a silk dress, which mother had believed would do no harm, in view of her good health for so long a period.

CASE II

Female, age 21. Eczema began in December when patient was aged 3 years, continuing till May. Began again following October, continuous thereafter. Face, neck, arms and legs affected during first attack, later entire body surface. Visits to seashore in summer brought some relief, which, however, lasted only 2 weeks after leaving. Patient reports that face and neck feel hot upon arising that there is white discharge on pillow. Condition is aggravated during 2 weeks prior to onset of menstruation, but does not clear up entirely at any time. Last 2 years, there has also been considerable sneezing.

Upon investigation, skin over entire body was found to be indurated and rough with many vesicles, pustules and areas exuding serum. A suitable allergen-free diet was prescribed. Within 10 days, patient reported skin of face and neck had cleared up completely, with body skin thinner and with less itching. At this time, improvement was interrupted by an attack of acute coryza, during which her face and neck again became hot, red and rough. Four weeks later, however, skin condition was completely cleared up, sneezing had stopped, and patient stated her general health to be better than for years.

At the end of 18 months, there had been no recurrence.

CASE III

Female, age 29. Eczema, which started at age 19, involved entire body surface. Upon examination, skin was found to be thick, very rough and scaly. Face and neck showed large denuded areas, with blood and serum exuding. Wrists and hands showed many fissures, some as much as $\frac{3}{8}$ inch deep; hands greatly swollen. Past year, patient has been forced to keep hands bandaged because of bleeding and exudation, which was sometimes so great that hands had to be held over receptacle because dressings became soaked through in a few minutes.

Patient showed very marked reaction to cat hair; large, extremely itchy wheal developed with great rapidity. Patient indicated that reaction occurred when she was merely in a house where cats lived, even though they did not come in the same room with her.

By following allergen-free diet and avoiding contact with cats, marked improvement was obtained in 10 days. In six weeks, patient's skin was found perfectly normal. There had been no recurrence at the end of three years.

It is interesting to note that this patient had been tested by an "allergist" prior to visiting me, and had been pronounced "not sensitive to anything."

CASE IV

Female, aged 29. This patient's symptoms began 16 years ago, with small spot of eczema on one arm. Over the years, condition progressed gradually, to include first one arm, then the other, next her neck and face, and finally her entire body. Perspiration, contact with silk or horsehair (mattress), or with rag, weed pollen, all seemed to aggravate her trouble. A visit to the tropics did not relieve symptoms. An attack of pneumonia did, however, produce relief during week that her temperature was high. Five years prior to this illness, patient had had partial gastrectomy for gastric ulcer and hemorrhages, following which she had to eat all meals in

bed, because, if she tried to eat sitting up, her heart action became very rapid.

Cutaneous tests showed reactions to certain foods, to horsehair, silk, rag weed. Ten days after starting prescribed diet, cardiac symptoms and nausea disappeared. Itching was 50% relieved in 2 weeks. In 5 weeks, skin was normal.

CASE V

Male, aged 54. Eczema for 6 years, starting on one finger, progressing to involve both hands, then inner canthus of one eye, finally covering whole face, neck and ears. Marked swelling of entire affected area. Had several attacks so severe that he was confined to bed for periods as long as 3 months. Two such attacks in one summer, otherwise condition usually worse in winter.

History shows that in 1915, patient had had an attack consisting of headache lasting 2 hours, followed by blurred vision, 1 hour. These symptoms reappeared about once a week for 2 years. In 1918, reported feeling tired, weak, exhausted; great depression, very difficult to get started doing anything, never felt warm. At age 28, had an attack of arthritis.

Upon examination, patient's face, neck, eyelids and hands were extremely swollen and red, with oozing serum.

Patient reported by letter, 3 weeks after starting prescribed diet, "skin condition completely cleared up—feel fine—no weakness, exhaustion, or depression—no gas, no headaches or blurred vision . . ." Six weeks later, patient's wife reported he was better than for many years.

CASE VI

Male, aged 49. First consulted, 1914. Showed redness and swelling of entire face, neck, eyelids, ears and hands. This condition had appeared during August and September (rag weed season) for preceding 10 years. Had "indigestion" 15 years. Diet and rag weed injections relieved all symptoms. In 1924, this patient again developed eczema and rag weed dermatitis, which was again relieved by same treatment as before.

In 1932, this man fell into the hands of the aforementioned "allergist," who tested him and pronounced him not sensitive to rag weed. However, after start of rag weed season, patient again came to me with severe dermatitis; showed marked reaction to rag weed!

PRURITUS

Is defined as a functional defect of innervation, in which itching is the only direct symptom. The term is usually used, not in reference to the symptom of such skin diseases as eczema, urticaria and the like, but rather to those conditions in which the sensation of itching, tingling, formication or something similar, is the sole trouble complained of. Lesions caused by scratching are secondary; the skin *looks* normal otherwise. The severity of the sensations may vary all the way from mild inconvenience to misery almost less endurable than actual pain, inducing mental depression or even actual insanity.

Pruritus is always worse at night or when subjected to extremes of temperature. Crocker says: "Pruritus is a sensory neurosis, due to direct or reflex irritation of any part of the nervous system, from the center to the periphery of the part affected, and not accompanied by any appreciable lesion of the skin nerves, but the presence of epithelium appears to be essential, as in the familiar instance of wounds which do not

itch until epithelium appears." Crocker's treatment depends upon the cause; unless this is discovered, success is unlikely. In the line of therapeutic efforts, internal treatment may be both dietetic and medicinal.

CASE VII

Male, aged 57. Pruritus, 2 years, affecting entire body, but worse in axillae, pubic region and over coccyx; itching, burning; worse in overheated rooms, in bed at night, and after exertion. Gave history of occasional headaches, indigestion, gas distress. Father had eczema. This patient's allergen proved to be pepper—even minute amounts produced marked symptoms within half an hour. Prescribed diet relieved all symptoms in 2 weeks.

CASE VIII

Female, aged 60. Pruritus, entire body, 2 years. Both lower legs showed marked redness, oozing of blood and serum, ulcers over tibiae and internal malleoli, which had existed for 1½ years. Patient had been forced to sleep without clothing or covering because of severe itching and burning of entire body. All symptoms were steadily increasing in severity. Prescribed diet reduced symptoms except on legs in 48 hours, to such extent that patient could return to normal sleeping habits. In 2 weeks, itching and inflammation of legs had disappeared; ulcer healed completely in 2 months. At this time, patient ate half an apple—one of her allergens—and suffered recurrence of itching within 4 hours which lasted 48 hours.

CASE IX

Male, age 50. Consulted for severe, continuous itching between shoulder blades, of 3 years' duration. Also reported that for 20 years he had seen a black spot continuously, at outer edge of right eye. After 2 weeks on prescribed diet all symptoms had disappeared. Six months later there had been no recurrence.

URTICARIA

Commonly called "hives," this condition affects young and old, male and female, with equal venom. Causes are most diverse—foods, medicines, insect bites, pollens, metals, cosmetics, among others. The possible external causes are almost as numerous as the external agents that can irritate the skin. Vidal excised a wheal during life, which showed both superficial and deep vessels dilated and engorged, without alteration of the vessel walls. Both blood vessels and lymphatics were surrounded by leucocytes, which were also found scattered in masses throughout the whole thickness of the cuticle. At certain points a few were also to be seen between the cells in the deepest layer of the epidermis.

CASE X

Female, aged 21. Urticaria over entire body and face, 1 year. Aggravated by friction, with severe burning sensation. History of severe, throbbing headaches, over vertex, dull aching over eyes, coming on in the morning, lasting all day. Also reports indigestion, gas, bad breath, every day, and that she tires easily. Allergen free diet produced improvement in 1 week, complete relief of all symptoms in 2 weeks.

CASE XI

Female, aged 20. Urticaria with rough and greatly thickened skin. This patient had consulted me 2 years previously, for life-long asthma, which had been completely relieved by diet. A new diet brought complete relief from skin condition also, within 2 weeks.

CASE XII

Female, aged 22. Urticaria on face, neck, abdomen, 6 years. Marked swelling of lips, eyelids, fingers and feet. History showed grandmother had had asthma; brother, hay fever. Allergen-free diet gave complete relief in 2 weeks.

CASE XIII

Male, aged 29. Angioneurotic edema, together with urticaria over entire body, 10 years. At intervals, tongue would swell till it protruded between lips, occasionally as long as 24 hours at a time. History showed father had had gastric ulcers. Diet relieved all symptoms within 2 weeks, but they would return with any lapse from prescribed regimen.

CASE XIV

Male, aged 22, medical student. Giant urticaria and asthma, which patient knew to be caused by eating any vertebrate fish, or coming in contact with any fish derivative such as glue, or mucilage on postage stamps. Shellfish did not affect. On one occasion, sat on spilled fish glue; marked swelling of buttocks in 10 minutes. "Oyster" stew made of cod-fish produced both giant "hives" and asthma within 15 minutes.

CASE XV

Female, aged 40. Urticaria on face, neck and body. Had been treated 6 months by dermatologist for what he diagnosed as scabies. Patient stated he had only looked at her hands. First visit made late at night because patient could not sleep for her misery. Hypodermic of adrenalin chloride gave relief in 15 minutes. After subsequent tests, diet gave complete, lasting relief in 10 days.

CASE XVI

Female, aged 89. Urticaria, 5 years. Began on legs, spread to entire body. Worse at night, itching severe. Often dizzy, especially upon arising. Took cold very easily. Blood pressure: systolic, 180, diastolic, 90. Diet reduced "hives" to a few in morning within 2 weeks. In 3 weeks, complete relief, with blood pressure reduced to 140/70.

CASE XVII

Male, aged 42. Urticaria, 6 years. Started on palms and soles, spreading in few days to whole body. Slight friction would cause patches to "run all together." No seasonal variation except worse in summer, past 2 years. Feet so swollen patient could not put on even extra-sized shoes before noon. Non-allergenic diet gave complete relief in 3 weeks.

CASE XVIII

Female, aged 54. Urticaria and angioneurotic edema, 10 months. Worse night and morning; severe swelling, face, eyelids (eyes closed), tongue, pharynx—suffocating feeling. Severe attacks, 40 and 5 days prior to consultation; complete loss of voice during last attack. Had suffered headaches and dizziness, sensation of swaying when walking and stomach distress after eating, past 4 weeks. Diet produced complete cure in 2 weeks, with no recurrence.

ACNE

This term is used to designate those lesions, chiefly pustular, produced by inflammation, in and around the sebaceous glands and hair follicles. Whenever the duct of a sebaceous gland becomes occluded, inflammation is likely to follow. The severity of the condition is largely dependent upon the number of comedoes, or "blackheads," present, as it is around these little plugs that the inflammation begins, followed by red papules,

which soon become pustular. The condition of the whole is limited, in the majority of cases, to the face—chiefly cheeks and forehead—the neck, chest and back, and the shoulders.

CASE XIX

Female, aged 14. Acne on face, forehead, neck and back, 1 year. Began at first menstrual period, but later seemed not be related to menstrual cycle. History of headaches 2 or 3 days each week. After 2 weeks on prescribed diet, acne was much improved. Improvement arrested by attack of acute coryza, but in 5 weeks patient was completely relieved of both acne and headaches.

CASE XX

Male, aged 20. Intermittent acne on face and arms, 3 years. Condition somewhat relieved during summer vacations at beach. History of raising considerable mucus, 4 or 5 times daily, especially upon arising. Suitable diet produced complete relief of acne in 6 weeks. Recurrence for 10 days, 3 months later, following injection of typhoid vaccine.

CASES XXI and XXII

Females, aged 26 and 28, sisters. Acne, 10 years; so severe that they wore heavy veils in public. Upon consultation, I opened more than 25 pustular abscesses on each patient. Four weeks of suitable diet produced complete cure.

CASE XXIII

Female, aged 48, married. Acne, very extensive over face, forehead, neck, since age 18. Showed considerable scarring of face. History of sinusitis of antrum at time of onset of acne; headaches; tuberculosis of right eye treated by serum injections, 10 years; constant black spots before eyes; "tooting" noise in ears; asthma since age 16; always tired. Paternal grandmother, father and sister had also had acne. Suitable diet cleared up acne, asthma and "tiredness" in 2 months.

ERYTHEMA MULTIFORMA, ERYTHEMA
NODOSUM

These conditions are characterized by both local and systemic symptoms, which occur in acute attacks, each running a short course, with a marked tendency to relaps, at varying intervals. The local lesions are symmetrical, raised and of some depth. They are extremely diverse as to shape, size, degree of elevation, and color. They may become vesicular or hemorrhagic. Constitutional symptoms usually coincide with the onset of the eruption, and may include pain in the joints, head, neck, back or limbs; malaise, gastric disturbances, temperatures from 101 to 104 degrees, increased pulse; the whole giving picture that may lead to suspicion of rheumatism.

Perry holds that erythema nodosum must be regarded as a result of a nonspecific reaction to a variety of infections or toxic reagents, rather than as a specific disease itself. However, it is clear that such agents or reagents can and do give rise to the syndrome only in patients constitutionally predisposed to such reactions.

CASE XXIV

Male, aged 23. At time of consultation, this patient had large, swollen mass, size of hen's egg, on lower part of left arm, with much swelling, edema, whole length

of arm and hand. Mass bright red, shiny, tense, very sensitive to touch.

History: vesicles from waist down, 4 years ago, followed by intermittent attacks of boils, as many as 48 at one time. Humming noise in right ear at intervals. Has always been hoarse at intervals; cough every morning, sometimes raised mucus. Has not felt well past 4 years: tired, sleepy, though sleeps well nights. Crepitation, both knees.

Three weeks after starting prescribed diet, swelling and induration had cleared up completely, feeling of being tired and sleepy completely gone. Two years later, there had been no recurrence of inflammation, swelling, boils or systemic symptoms.

CASE XXV

Female, aged 48, married. Consulted for inflamed areas on both arms and hands; hard, indurated, extending into deep tissues, very tender, varying in size from walnut to hen's egg.

History: asthma in childhood; urticaria, 4 years; hysterectomy, 6 months; 3 weeks previously, sharp pain in cardiac region, "purple in the face," could not breathe, ankles greatly swollen, painful; chills every night first 30 minutes in bed; since cardiac attack, dry cough and "tired feeling."

Examination showed arthritis in cervical vertebrae, both sacroiliac articulations, knees, both ankles; marked varicose veins, both legs; on inner side of left leg above ankle, large area markedly bronzed, indurated, tender, with ulcer formation.

Four days after starting prescribed diet, 2 new areas just below one knee, showed inflammation, induration and swelling to size of walnut. However, older areas improved steadily. Four weeks after starting diet, patient was entirely free of pain and swellings.

FURUNCLES WITH ECZEMA SCLEROSUM

CASE XXVI

Female, aged 28. Furuncles and carbuncles, over entire body, 6 years; excised as they appeared.

History: eczema since age 9, on hands and feet, spreading to knees, elbows, finally entire back; worse in winter.

Examination showed large scars from occiput to coccyx, also on chest, legs, abdomen. Palms and soles, thick, hard, boardlike, indurated. (Eczema sclerosum).

Furuncles and carbuncles continued to appear for first 3 weeks after starting prescribed diet, but patient reported at end of 6 months, condition was completely cleared up, with palms and soles also returned to normal.

PSORIASIS

This is a chronic inflammatory disease, characterized by dry, red patches covered with imbricated, silvery, adherent scales. These occur chiefly on the extensor surfaces, but may appear on any part of the body, face or scalp.

CASE XXVII

Male, aged 40, clergyman. Psoriasis on back and extensor surfaces of arms and legs; extreme itching; thick, silvery scales, 3 months.

History: acne, back and lumbar region, 25 years. Headaches, lasting 2 days, about every 2 weeks, past 20 years. Thick, reddish, disagreeable-tasting mucus in mouth on arising; gas after meals; always tired. Father had asthma and bronchitis.

Suitable diet produced improvement in all symptoms in 2 weeks, complete relief in 6 weeks.

CASE XXVIII

Female, aged 42, married. Psoriasis on abdomen, chest, feet, legs, about rectum; also sore mouth, mucous membrane coming off, especially inside lips; last 4 months. Margins of eyelids inflamed. Left side of nose always blocked, right side at intervals. Burning sensation in stomach after eating. Dizziness lasting 15 minutes upon arising. Cardiac pain.

History: arthritis; cervical, dorsal, sacro-iliac, knees, hands, feet, past 15 years. Headaches; gnawing pain in occipital and frontal areas, usually on left side, often lasting a week at one-week intervals; also roaring in ears and sore left eyeball; past 6 years. Past 2 years, tired, exhausted, depressed.

After 23 days on prescribed diet patient reported by letter, "skin much better, scales and red spots have practically disappeared — physically. . . better, no pain around heart, free of all joint pains, not tired. . ."

CASE XXIX

Female, aged 35, married. Psoriasis, lasting 5 months, began 6 years ago, 2 days after birth of first child. Recurred 3 days after birth of second child, 21 months after first. Affected abdomen, back, hands, feet, extensor surfaces of arms and legs.

History: eczema in childhood. Tired for years, more so since births of children. Sister has psoriasis; mother had arteriosclerosis, arthritis, headaches.

25% improvement of psoriasis after 2 weeks on diet; 6 weeks, 70%; 10 weeks, showed complete freedom from psoriasis; patient no longer tired.

CASE XXX

Female, aged 18. Psoriasis on scalp, spreading to abdomen, back, buttocks, chest, legs, arms, at age 8. Treated at hospital clinic for 6 years; following injection into buttocks, face also became involved. Condition has increased steadily in severity, being worse in winter.

At time of consultation, patient had no normal skin in affected areas; scales $\frac{1}{8}$ inch thick covered chest, abdomen and back from axillae to lower margins of tenth ribs; also from anterior superior spines of ilium across back and over buttocks.

After 2 weeks on prescribed diet, patient's face was clear. In 3 weeks, there was a 50% improvement over other affected areas, with scales much thinner; in 12 weeks, she was completely free of scales, her skin normal.

CONCLUSIONS

1. Such dissimilar conditions as eczema, pruritus, urticaria, acne, psoriasis, erythema and angioneurotic edema are discussed and summarized, in their relation to allergies.

2. Thirty cases are presented, all of which yielded satisfactorily to treatment of which the chief feature was the prescribing of a diet free from foods to which each individual was sensitive. In several of these cases, additional precautions, resulting from evidence of sensitivity to substances other than foods, were also needed, some only temporarily.

3. In a notable number of the cases presented, long-standing conditions, some not usually connected in the mind of the diagnostician with sensitizations, were cleared up in a remarkably brief period.

4. Several of these patients had been unsuccessfully treated by other methods over varying periods of time.

REFERENCES

- Crocker, H. R.: Diseases of the Skin. 3rd Ed., 2 Vols., Phila.: P. Blakistons' Sons & Co., 1910.
- Perry, C. B.: Aetiology of erythema nodosum (Bradshaw lecture). Brit. M. J., ii:843-847, Dec. 30, 1944.
- Turnbull, John A.: Allergy as a factor in thrombosis. Am. J. Dig. Dis., X:184-188, May, 1943.
- Idem.: Tired, weak, exhausted, depressed patient. Am. J. Dig. Dis., X:218-224, June 19, 1943.
- Idem.: Allergy as a factor in surface ulcers, varicose veins, phlebitis, and thrombosis. Am. J. Dig. Dis., XII:272, August 1945.
- Videl, E.: De l'urticaire. Ann. de Dermat. et Syph., I:408, 1880 (Abstr. in Lancet I:537, 1880).

Diverticula of the Colon Versus Gallstones

By

ARNOLD GALAMBOS, M.D.

and

WILMA MITTELMANN-GALAMBOS, M.D.

NEW YORK, N. Y.

THE large-intestinal diverticula are most commonly found in the sigmoid and descending colon. In far advanced cases as well as in generalized diverticulosis the entire colon may be affected, although with unequal distribution: the most densely involved areas still being in the vast majority of cases the above mentioned locations. Diverticulosis has relatively rarely been found isolated at some other than the aboral segments of the colon, as the appendix, or the cecum, or some other segments of the gut. Cases of diverticulosis located at the hepatic flexure, with their visualized images projected at the gallbladder area must be considered rare.

In these few lines we wish to report a case of intestinal diverticulosis, in which the area containing the diverticular sacculations remained confined to a circumscribed segment around the hepatic flexure, though few isolated diverticula extended also into the adjoining portions of the colon; the typical locations in the distal half of the colon remained completely free. After our first rectal barium filling the opaque material, contained and retained in the diverticula, projected its shadow exclusively at the site of the gallbladder region. The x-ray photography revealed these diverticular projections as rounded or faceted, opaque, in some, even as cortically denser shadows, being suggestive of calcium containing gallstones.

This patient has been suffering in addition to diverticulosis of the colon also from cholelithiasis. The history of cholelithiasis and the Graham-Cole's cholecystography by failure to visualize the gallbladder, seemed to furnish corroborative evidence of the co-existence of cholelithiasis. Consequently the shadows produced by the barium-filled colonic diverticula, being projected at the site of the gallbladder region and being characteristic of the well known gallstone pictures, might have been easily taken as positive evidences of gallstones. Subsequent examinations in an hour's time, however, revealed the fallacy of such diagnosis, if made on the first impression, inasmuch as the spurious stone shadows proved to be barium filled colonic diverticula, while the actually present non-opaque gallstones did not cast shadows on the film.

CASE REPORT

Y. J., white, female, aged 50, first seen on the 21st of November, 1944. She has been suffering for the last four years. Abdominal distress, inconclusive gastrointestinal vague complaints, such as nausea, occasional vomiting, heartburn, eructation of gases, constipation intermingled with such nervous symptoms as palpitation of heart, dizziness, general weakness, etc., were among the symptoms revealed in the history.

Since the last six months severe upper abdominal painful attacks developed and recurred at frequent intervals, in form of biliary colics. At no time was fever, jaundice or any long continued suffering or confinement to bed encountered.

Patient was highly neurotic. Her bodily symptoms kept her fully occupied. She lived under great emotional strain and was in constant anxiety and fear, at times even in fear of impending death.

Physical examination was largely negative. There was no tenderness, nor any pathological palpatory findings noted in the abdomen, except for some transitory tenderness of the gallbladder region, during and following an acute attack of cholelithiasis. Blood pressure was normal; fluoroscopy, electrocardiography during rest as well as on effort, laboratory examination of the urine and feces, etc., were all negative.

Röntgen examination of the gastrointestinal tract, including barium enema of the colon — during the series of examination — was negative (XI/22). No diverticula were noted (Fig. 1). On the post-defecational film, the barium largely being evacuated from the colon, partly regurgitated into the small intestines — a frequent occurrence, due to the insufficiency of the Bauhin valve. It was, however, noteworthy to mention, that no diverticula were noted even on the film after the defecational act, though this is being considered the most proper way to demonstrate diverticula, if present (Fig. 2).

Four days later (XI/26) routine cholecystography has been made by the method of Graham-Cole, using three grams of priodax (Figs. 3, 4, 5). These films failed to visualize the gallbladder. There were, however, in the gallbladder region, and only there, sharply outlined shadows present, typical of the Ca containing gallstones. Both, failure to visualize the gallbladder and the presence of opaque stone-like shadows at the site of the gallbladder, were indicative of a chronic cholecystitis with cholelithiasis. That was the first impression here, too.

On closer view one could clearly distinguish at least six stones, or stone-like shadows, some of them so-called ringstones, the others homogeneous in appearance. Their shape, size, appearance, location, constellation, even a greater peripheral opacity on some, etc., were all in conformity with characteristics of gallstone shadows (Fig. 3).



Fig. 1 — Barium enema. No diverticula seen.

On checking up on these findings — by using slightly different technic — a second film (Fig. 4) produced a practically identical picture. However, on a third film — maybe an hour later — surprisingly, certain definite changes were noted (Fig. 5). The opacity of some of the shadows diminished, the number of the well visualized stone-like shadows became reduced from six to four and their constellation changed.

DISCUSSION

It was only too evident that the features described above were incompatible with the assumption of gallstones. Disappearance, or emptying of the opaque shadow before our eyes, in the course of an hour or so, as observed on the serial photography, was easier amenable to explanation by assuming the presence of barium-filled diverticular sacculations. Subsequently the correctness of this diagnosis has amply been proven. It was evident, that during the first series of examination, the barium content of the diverticula must have been derived from the regurgitated portion, which, after re-entering the colon, has been retained in the diverticular sacs and demonstrated through x-rays.

The film presented under Fig. 6 is the *typical* picture of the case, as far as the distribution of the diverticula is concerned. Several re-examinations resulted in similar pictures. As demonstrated by this film, the greatest number of diverticula was located at or around the hepatic flexure, with the projection of

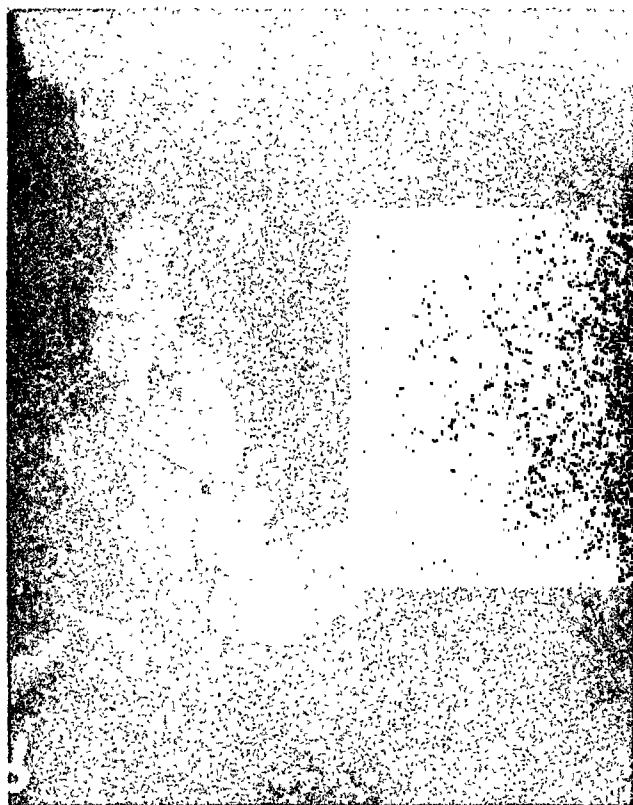


Fig. 2 — Barium enema. Post-defecational film.

their visualized images at the gallbladder region, whereas other diverticula were seen scattered along the ascending and transverse colon, too. At no time were any diverticula noted along the sigmoid or descending colon.

The x-ray pictures taken have been found "typical" in every case, during the repeated re-examinations, regardless of whether the barium has been taken by the oral or by the rectal route. The diverticular shadows usually — once shown — remained visualized, persistently, for days and weeks. One film, taken two months after the last barium intake, failed to show the presence of any diverticula, any more.

The results of the *first series of examination* as compared with the ones obtained during the repeated re-examinations, described as *typical* pictures, differed in several respects. The first examination, respectively, its results represented exceptional findings. That was due to certain *coincidental* factors, the presence of which created at least *three unusual features*, the recognition and proper evaluation of which enabled one to arrive at a correct diagnosis at a correct time.

1) During the first examination the diverticula were not visible, not even on the post-defecational film. Only a few days later, when the barium, which regurgitated into the small intestines, after re-entering the colon, acceded into the diverticular sacs and incidentally has been photographed during the performance of the cholecystography, did we note their presence, unexpectedly. One expected gallstones during the chole-

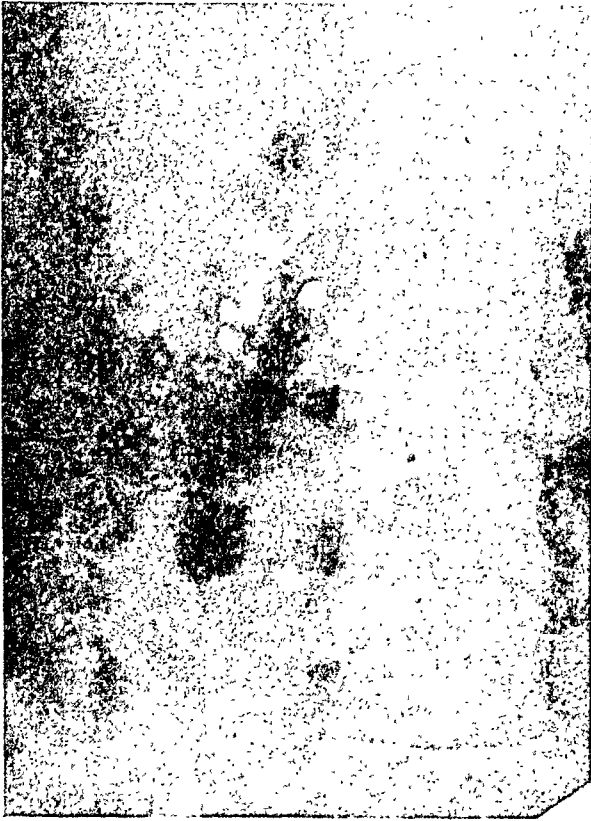


Fig. 3 — Cholecystography. Gallbladder not visualized. Six stone-like shadows at the gallbladder region, representing barium-filled diverticula of the colon.



Fig. 4 — Similar film. Taken a few minutes after the previous one. Note that Fig. 4 and Fig. 3 are nearly identical.

cystography and one found gallstone-like shadows. proven later not to be gallstones.

During the control re-examinations the diverticula were always easily recognizable, right on the post-defecational films.

2) A further coincidence was presented by the fact that, during the first examination, the barium entered the diverticula not only *belatedly*, but at the same time, only *partially*. Through this coincidence *only* those diverticula were entered and became roentgenologically demonstrable, which projected their images at the gallbladder region. No other diverticular shadows were seen. Why and how this happened, remains an enigma.

During the repeated re-examinations, diverticula were seen beside the gallbladder region, also scattered along the ascending and transverse colon.

3) A still further coincidence was seen by the fact that, during the first examination, within an hour's time, signs of emptying of some of the diverticular sacs were noted, enabling one to arrive at a proper interpretation of the findings.

During the repeated re-examinations the diverticula retained their barium contents for weeks, so the hourly changes must have been unnoticeable, as a rule.

The coincidence of the *late and partial filling* and *early partial emptying* of the diverticula during the first series of examination as against the routine behaviour

during the repeated re-examinations were contributory to the puzzle and perplexity and their proper recognition and evaluation in a short time helped to create a clear understanding of the situation and establishing a correct diagnosis, without any loss of time.

Should any gallbladder surgery been resorted to on ground of a diagnosis made on the very first impression, when the stone-like shadows were first seen, the surgical indication could not have been sustained in view of the subsequent developments. However, in final analysis, such surgery could have had quite a salutary effect. While it is true that the possible incentive for surgical indication, namely, the presence of stone-like shadows in the gallbladder region, soon proved to be diverticular sacculations of the colon, requiring no surgery, on the other hand the removal of the gallbladder with its roentgenologically invisible, non-opaque stones might have solved the patient's problem. So far no operation has been suggested.

SUMMARY

A case of diverticulosis of the colon is presented with an unusual location of the diverticula. The barium filled diverticula projected their shadows at the site of the gallbladder region.

These shadows appeared in the shape, size, location, constellation, including even certain ringshape formation of the characteristic x-ray picture of gallstones.

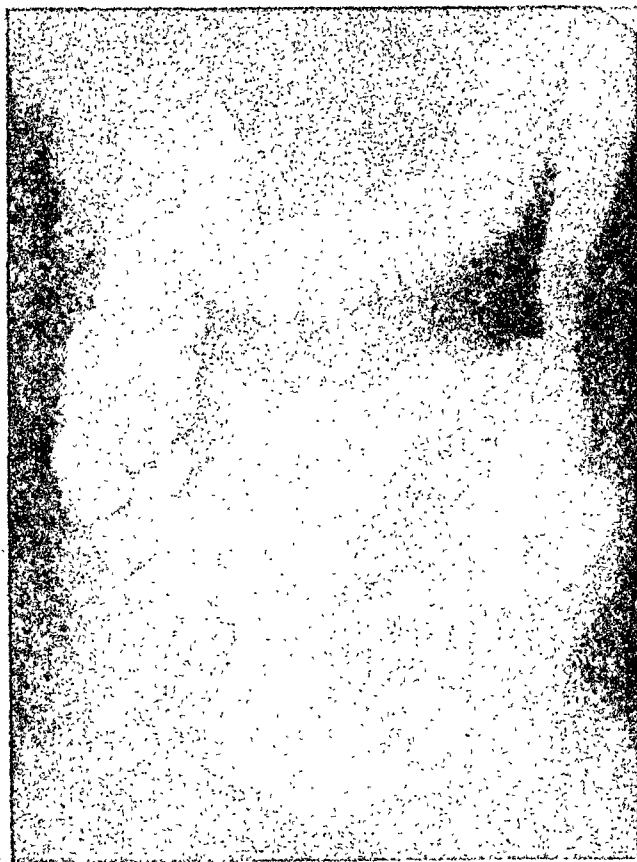


Fig. 1 — Barium enema. No diverticula seen.

On checking up on these findings — by using slightly different technic — a second film (Fig. 4) produced a practically identical picture. However, on a third film — maybe an hour later — surprisingly, certain definite changes were noted (Fig. 5). The opacity of some of the shadows diminished, the number of the well visualized stone-like shadows became reduced from six to four and their constellation changed.

DISCUSSION

It was only too evident that the features described above were incompatible with the assumption of gallstones. Disappearance, or emptying of the opaque shadow before our eyes, in the course of an hour or so, as observed on the serial photography, was easier amenable to explanation by assuming the presence of barium-filled diverticular sacculations. Subsequently the correctness of this diagnosis has amply been proven. It was evident, that during the first series of examination, the barium content of the diverticula must have been derived from the regurgitated portion, which, after re-entering the colon, has been retained in the diverticular sacs and demonstrated through x-rays.

The film presented under Fig. 6 is the *typical* picture of the case, as far as the distribution of the diverticula is concerned. Several re-examinations resulted in similar pictures. As demonstrated by this film, the greatest number of diverticula was located at or around the hepatic flexure, with the projection of



Fig. 2 — Barium enema. Post-defecational film.

their visualized images at the gallbladder region, whereas other diverticula were seen scattered along the ascending and transverse colon, too. At no time were any diverticula noted along the sigmoid or descending colon.

The x-ray pictures taken have been found "typical" in every case, during the repeated re-examinations, regardless of whether the barium has been taken by the oral or by the rectal route. The diverticular shadows usually — once shown — remained visualized, persistently, for days and weeks. One film, taken two months after the last barium intake, failed to show the presence of any diverticula, any more.

The results of the *first series of examination* as compared with the ones obtained during the repeated re-examinations, described as *typical* pictures, differed in several respects. The first examination, respectively, its results represented exceptional findings. That was due to certain *coincidental* factors, the presence of which created at least *three unusual features*, the recognition and proper evaluation of which enabled one to arrive at a correct diagnosis at a correct time.

1) During the first examination the diverticula were not visible, not even on the post-defecational film. Only a few days later, when the barium, which regurgitated into the small intestines, after re-entering the colon, acceded into the diverticular sacs and incidentally has been photographed during the performance of the cholecystography, did we note their presence, unexpectedly. One expected gallstones during the chole-



Fig. 3—Cholecystography. Gallbladder not visualized. Six stone-like shadows at the gallbladder region, representing barium-filled diverticula of the colon.

cystography and one found gallstone-like shadows, proven later not to be gallstones.

During the control re-examinations the diverticula were always easily recognizable, right on the post-defecational films.

2) A further coincidence was presented by the fact that, during the first examination, the barium entered the diverticula not only *belatedly*, but at the same time, only *partially*. Through this coincidence *only* those diverticula were entered and became roentgenologically demonstrable, which projected their images at the gallbladder region. No other diverticular shadows were seen. Why and how this happened, remains an enigma.

During the repeated re-examinations, diverticula were seen beside the gallbladder region, also scattered along the ascending and transverse colon.

3) A still further coincidence was seen by the fact that, during the first examination, within an hour's time, signs of emptying of some of the diverticular sacs were noted, enabling one to arrive at a proper interpretation of the findings.

During the repeated re-examinations the diverticula retained their barium contents for weeks, so the hourly changes must have been unnoticeable, as a rule.

The coincidence of the *late and partial filling* and *early partial emptying* of the diverticula during the first series of examination as against the routine behaviour



Fig. 4—Similar film. Taken a few minutes after the previous one. Note that Fig. 4 and Fig. 3 are nearly identical.

during the repeated re-examinations were contributory to the puzzle and perplexity and their proper recognition and evaluation in a short time helped to create a clear understanding of the situation and establishing a correct diagnosis, without any loss of time.

Should any gallbladder surgery been resorted to on ground of a diagnosis made on the very first impression, when the stone-like shadows were first seen, the surgical indication could not have been sustained in view of the subsequent developments. However, in final analysis, such surgery could have had quite a salutary effect. While it is true that the possible incentive for surgical indication, namely, the presence of stone-like shadows in the gallbladder region, soon proved to be diverticular sacculations of the colon, requiring no surgery, on the other hand the removal of the gallbladder with its roentgenologically invisible, non-opaque stones might have solved the patient's problem. So far no operation has been suggested.

SUMMARY

A case of diverticulosis of the colon is presented with an unusual location of the diverticula. The barium filled diverticula projected their shadows at the site of the gallbladder region.

These shadows appeared in the shape, size, location, constellation, including even certain ringshape formation of the characteristic x-ray picture of gallstones.

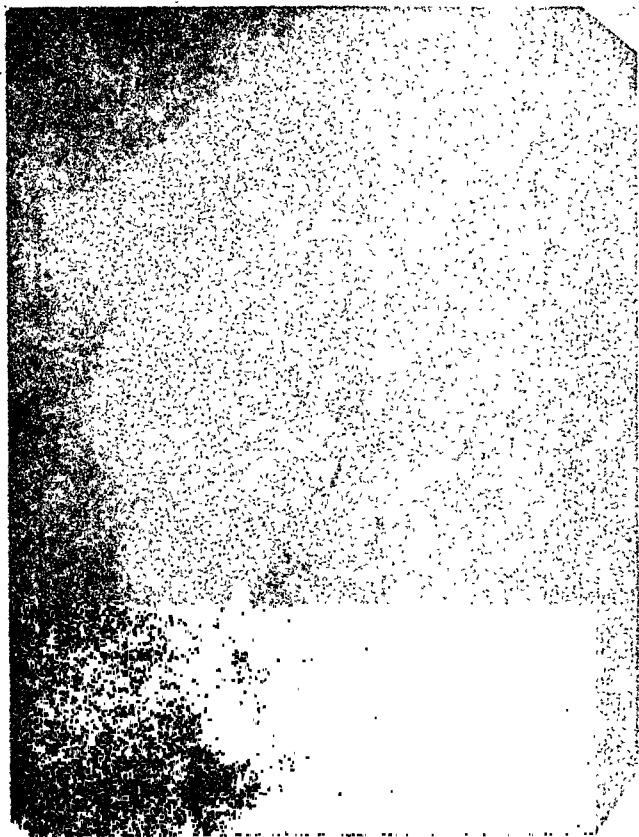


Fig. 5—A third film. Taken about one hour later. Note the number of the opaque shadows being reduced from six to four.

Subsequent films, on close inspection, revealed certain changes inconsistent with gallstones, but easily explainable by diverticular sacculations.

Patient suffered, incidentally, from a superimposed cholelithiasis, too, as evidenced by the typical history and the failure to visualize the gallbladder and its contents by the routine method of cholecystography.

The projected gallstone-like shadows on first im-

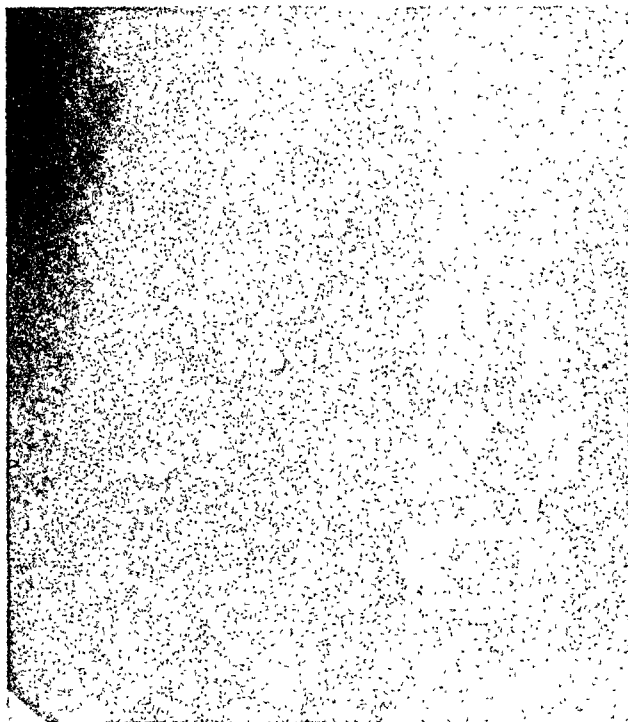


Fig. 6—Diverticula of the colon, along the ascending and transverse colon.

pression might have been conducive to be considered gallstones, responsible for the recurring severe biliary attacks. However, these shadows proved to be barium-filled diverticular sacculations, with their shadows projected at the gallbladder region, while the gallstones, responsible for the attacks, being non-opaque and invisible to x-rays, failed to be visualized and consequently demonstrable through x-rays.

Various coincidental factors created a diagnostic puzzle and perplexity. Their proper recognition and interpretation, however, enabled the establishment of an early and correct diagnosis.

Gastric Carcinoma: Review of Errors in Diagnosis

By

MEYER GOLOB, M.D.
NEW YORK, N. Y.

THE points to be considered in this paper are: 1) age incidence; 2) length of history; 3) size and site of lesion and their influence on early diagnosis; 4) malignant degeneration of benign gastric ulcer. These captions were chosen because they figure in wrong interpretation of symptoms and thus to delay in diagnosis of gastric malignancy.

There can be no doubt that the first stage of a disease is the best time for cure. Early diagnosis is conducive to timely intervention. But diagnosis early in point of examination might yet reveal advanced pathology and, therefore, no longer be timely for surgery. The clinician sees the patient either in the initial stages

or in full swing of the malady, the pathologist surveys the terminal event. The first stages are probably reversible. Detection at this time is the task of the clinician. Knowing this, believing this, why do physicians delay? Alvarez (1) asks, "How early do physicians diagnose cancer of the stomach in themselves?" His analysis of 41 cases, all operated upon, is not productive of complacency. In a vast number of cases the patient alone is responsible for delay, in many instances both patient and doctor are to be blamed, but in not a few the doctor alone is accountable for depriving the patient of both an early diagnosis and a timely diagnosis and intervention. A reasonable general appraisal of responsibility for delay in diagnosis of carcinoma holds patients alone responsible in about 55%

of the cases, physicians alone in some 17%, and both doctors and patients in the remainder.

On the whole the explanation is only too obvious: the so-called classic syndrome of gastric cancer is not volunteered by the patient and none of the components of the syndrome is specifically enquired for by the examiner and none related by the patient. In a vast number of cases symptoms should and could be elicited through a really searching and persistent inquiry. Some patients are subclinical individuals, and thus offer stumbling blocks to early diagnosis. If this were borne in mind, the wary physician would be more on the alert, question more persistently in the elicitation of symptoms, and through such an approach reduce a far distant horizon to a clinical recognition of an incipient malady. If pre-clinical medicine were included in our medical curricula where it rightly belongs instead of being made to wait for occasional post-graduate training, a greater portion of subclinical cases would not escape timely detection. A study of a large series of autopsies has shown that a far greater percentage of ulcers or scars of ulcers was found in the stomach than in the duodenum, with the inference that gastric ulcers more readily escape diagnostic discernment than do duodenal ulcers — compelling testimony of the need for early diagnosis in gastric lesions.

Lesser gastric curvature ulcers are of course predominantly attended with hyperchlorhydria, bear potentiality for malignant degeneration and, therefore, indicate a close follow-up. On the other hand, cases of achlorhydria, particularly familial, even more pointedly require continued clinical observation. In five of my cases which were closely observed, two were of a family of four, and the terminal events were those of gastric cancer. Unfortunately, the other two members of this achylia family escaped observation.

In final analysis, an adequately taken history serves as a precision instrument in diagnosis. No new information is offered by this statement, but such that can bear repetition and reiteration. It can be said that patients with benign ulcers tend to have long histories, while those with cancer tend to have short ones. When a long history presents itself with a decrease in remissions and accentuation of symptoms, transformation of benignity into malignancy is to be expected.

The cases reviewed for the purpose of this paper are from the writer's private practice and they present the features enumerated above. They illustrate that neither the age of the patient, nor the presence of achlorhydria or hyperchlorhydria, nor — a point which cannot be overemphasized — the size of a gastric lesion should lessen our suspicion of gastric carcinoma. To assume benignity because of diminution in size, and clinical response to treatment is hazardous. Practically every early case of gastric cancer, when treated medically for ulcer, shows relief of clinical symptoms for a time. Thus it is dangerous to depend on a therapeutic test for proving a lesion benign. Diagnosis is surely more convincing when based on the combination of roentgenology and clinical evidence. However, when the two are at variance, greater dependence should be

placed on the latter. Thus the task of early diagnosis, as stated, necessarily falls on the clinician, and the instrumental approach, and that is what roentgenology means, is largely an exposé of advanced pathology. It is, therefore, up to the symptomatologist and the historian of the case to make an early and timely diagnosis. Major criteria for diagnosis are, of course, convenient and preferable to minor criteria, but in their absence, the latter assume major diagnostic significance. To wait until the whole ensemble of classic signs and symptoms present themselves is a dangerous approach in the assessment of a gastric lesion.

ILLUSTRATIVE CASES

Case 1 (age incidence): Male, aged 37, presented himself in January, 1936. He related gastric upsets, not descriptive of either a pre- or post-pyloric lesion, of 8-10 years' duration. Seven years before he had had uncontrollable vomiting, attended with abdominal pain, for one week. The presenting symptomatology dated to November, 1934. The patient emphasized the following: anorexia, weight loss and progressive asthenia. Comfort paralleled abstinence from food intake. The history also revealed that he had a hypochlorhydria which moved to achylia — an indication of a progressive lesion and more related to an intra- than to an extra-gastric lesion. However, an "extra-gastric" condition was argued by those who spared the rod and ruined the child. The Consultation Service of the Mount Sinai Hospital reported to the referring physician (December, 1934) that the roentgenological examination of the gastrointestinal tract revealed the presence of an irregular constricting lesion of the pre-pyloric segment, interpreted as probably malignant. An irregularity of the bulb suggested the possibility that the constriction of the antrum might have been owing to an old stenosing ulcer. Immediate exploratory laparotomy was advised. But — despite the hospital survey, despite absence of circumstantial x-ray evidence of involvement of the pancreas and other adjacent structures, despite the fact of the pre-pyloric antrum shown to be canalized and devious, unlike the concentric symmetry and non-tortuosity of syphilis of the gastric antrum — a well known gastroenterologist treated the patient with the reassurance too readily accepted by most ill persons. He was permitted to go on unoperated upon until January, 1936. Operative findings: cancer of the stomach. Pathological diagnosis: anaplastic, infiltrating carcinoma (grade IV) with ulceration and metastasis to the regional lymph nodes. He was granted one year post-operative survival.

The stormy gastric disturbances early in his history might have been owing to a pre-pyloric ulcer which, as a benign lesion, unlike a primary malignant neoplasm, could trespass into the first portion of the duodenum. It is not uncommon to find a pre-pyloric defect with canalization and marked narrowing and a normally outlined bulbous duodeni; demonstrating the abrupt halt of a formidable lesion contrasting with a benign, inflammatory process which trespasses into the duodenum and also into the pre-pyloric region. The following must be noted: in the case of a lesser curvature lesion with an irregularly outlined bulb, instead of tending toward a diagnosis of multiple benign ulcers, it is far safer to think of the gastric lesion as probably malignant until proved otherwise — regardless of age. In the Mayo Clinic, 60% of gastric ulcers are treated surgically, because the chance of malignancy is greater than that of post-operative mortality. It may, of course, be argued that a much dilated stomach without criteria of anatomical destruction of the pre-pyloric segment speaks for an ulcer rather than a malignant lesion, when this is sup-

ported by other essentials in the study of the case. As illustration, in the case of a large gastric residue with roentgen evidence of irregularity of the proximal or basal portion of the cap — suggestive evidence of a pre-pyloric benign lesion bridging into the first portion of the duodenum — the operative finding was pre-pyloric ulcer. But the particular case under discussion, the writer believes, was a pre-pyloric ulcer, atypical in its clinical pattern, with the symptoms poorly interpreted.

The argument advanced in this case against an intrinsic gastric lesion is strikingly interesting in retrospect. The eminent physician reported: "... in all probability an extragastric lesion, perhaps cystic, which condition accounted for the five days of vomiting six years ago and which is again active." The patient was advised to go on with symptomatic therapy, however, "a surgical repair of the condition that presses on his pylorus will, in all probability be called for." Two months later he reported, "I can make no ulcer or malignant disease out of it and the films today as compared with films taken in the last two months show no progress in the condition. I have finally come to the conclusion that the case of X. Y. is a pressure on the pylorus from outside the stomach. . . ."

DISCUSSION

This case demonstrates the advisability of disregarding the age of the patient and of learning to respect disease in its initial phase of onset. The "insignificant symptoms" were not respected and passed unrecognized until a malignant syndrome announced itself, and even this was not adequately evaluated because the patient was "too young." Alvarez (2) notes that "... one of every nine patients with cancer of the stomach is less than 45." Another doctrine was available, however, one in which I was indoctrinated: when two diseases are possibilities, even with equal evidence for each, the chances favor the commoner of the two. Would an intrinsic gastric lesion, the commoner of the possibilities, have been considered primarily, the age of the patient itself, and the duration of symptoms, would have led to the inference that there had been a peptic ulcer, perhaps atypical in its manifestations, that had degenerated into malignancy. This was precisely the view advanced at the Mount Sinai Hospital: "There is an irregularity of the duodenal bulb, suggesting the possibility that the constriction of the antrum may be due to an old stenosing ulcer." In face of all this, uncertainty in diagnosis conveyed to the patient led to a delay of more than a year. The fact that his conservative adviser obtained alleviation of symptoms initially, calls to mind many cases the writer has encountered, with psychoneurosis in addition to somatic disease, in which assurance, nerve sedation medication and regulation of diet, relieved the patient of psychogenic symptoms with temporary alleviation of structural alteration.

What has been said of cancer of the colon, that when found in the younger age group it is usually of a violently malignant nature, with morbidity and mortality high, is equally applicable to gastric carcinoma. It may be observed, however, that high mortality is not engendered so much by virulence in youth as by the fact that the condition is for this reason of youth seldom considered a diagnostic possibility, and the disease

is far advanced by the time surgery is undertaken. It has been stated that of every 100 patients with gastric carcinoma entering American hospitals, some 50 are inoperable, 25 resectable, and 25 capable of only palliative surgery — a tragic situation indeed.

A survey of my referred cases demonstrated that age as a misleading factor played a great part in delaying diagnosis. Certain common expressions are to be deplored, such as the term "cancer age." In my very early writings I stated, "It is misleading and may produce a state of hypochondriasis in those of the so-called cancer age and also give rise to a false sense of security in those outside this period of life." All authorities agree that the greatest advance in the early diagnosis and treatment of gastric cancer can be accomplished by making the public and profession alike "cancer minded," prepared to consider the possibility of malignancy with but vague indications of this disease. Gastric carcinoma may occur at any age, and the so-called cancer age is much less valuable as a diagnostic criterion than the minor digestive symptoms that are so frequently associated with the disease.

I write these lines with some hesitancy, since I believe their intent is somewhat trite and threadbare to many a reader of medical literature, but I do wish to reach the novice in medicine. Vagueness in symptoms in cancer of the stomach is to be regarded as a definite presentation of the malady with persuasive diagnostic properties. Hematemesis, impaired gastric clearance, palpable adenopathy are signs of complications, not of the primary disease itself. Absence of pain is no evidence that cancer of the stomach is not present and, the farther removed the growth is from the two extremes of the stomach — cardiac and pyloric segments — the later are symptoms likely to appear. Between these extremes is an anatomically silent area which, therefore, offers a silent symptomatology, unless the mass is in the neighborhood of the cardiac orifice, when some degree of dysphagia is an early symptom. Added to clinical silence, the belief of some that cancer is confined within the limits of a minimum and a maximum age is a concept which must be regarded as dangerous in the extreme. Richard C. Cabot (3) pointedly wrote a long time ago: "We are accustomed to say that when a patient past 40 years begins to have dyspepsia out of a clear sky — that is, without any obvious cause or any previous habit — cancer is the most probable diagnosis; but when saying this we must remember that the cancer age is also the arteriosclerotic age, and, therefore, the time for nephritis and uremia. Furthermore, the cancer age is also the gallstone age, and the age for angina pectoris." To halt the currency of this phrase among novice and, unfortunately, mature physicians would indeed aid in early recognition of subclinical or masked cases of gastric cancer. A conclusion of my earlier writings merits repetition. "It is the prediagnostic phase of cancer that we must endeavor to detect — a phase often disregarded because of lack of impressive signs or symptoms, as when neither the cardiac nor the pyloric orifice is involved, when there is no hesitation in food entrance

and no obstruction to food exit. A suggestive symptomatology, no matter how faint the indication, calls for a searching inquiry. Let us remember that the easier it is to diagnose malignancy, the harder it is to operate on it."

Case 2: Male, aged 64, presented himself with a textbook description of a malignant syndrome of the stomach. He was highly optimistic about regaining his health, because, on repeated x-ray examinations, "no pathology" had been found. But he looked for aid to ease his symptoms. One of the x-ray reports read: "There is no evidence of a filling defect in the cardia or in the fundus of the stomach." This report deserves more than passing reference, since the roentgenologist of a very prosperous commercial laboratory had made his survey only four days after a private physician had found unequivocal evidence of an advanced neoplasm of the cardiac third of the stomach. What is even more interesting in this case is that, owing to "smoothness," the lesion was interpreted as being either syphilis or sarcoma. The patient looked for a reversal of this diagnosis and, unfortunately, found it in the commercial laboratory. The loss of time was clinically too obvious. The surgical finding was inoperable carcinoma. In this instance the patient would have benefited had age incidence been considered as against either syphilis or sarcoma. Carmen (4) wrote, with reference to histological diagnosis: "When clinicians with whom I am associated press me for pathologic diagnosis in such cases — whether benign or malignant, carcinoma or cyst — I am in the habit of saying, 'I am sorry, but I have no microscope attachment to my x-ray machine.'"

Case 3: Male, aged 45, with occupation and family history non-contributory. The presenting symptomatology was of three months' duration, and had depicted a duodenal ulcer symptom complex which was, however, lacking in nocturnal episodes of pain. Periodicity was not evident, and the shortness of the history stood in bold contrast with the conventional long history observed in peptic ulcer. The gastric chemistry offered no evidence for a duodenal lesion. Since the clinical picture was not conclusive with respect to a peptic ulcer, and did not correlate with the gastric chemistry, the laboratory summary assumed great significance, and the short history arrested attention. The patient was re-x-rayed, about five weeks after the first roentgen study. The gastric antrum was suggestive of pathology, but none too persuasively. The re-x-ray showed a definite prepyloric lesion. The clinical picture had lost the rhythm of pain-food-ease. In lieu the patient cited a malignant syndrome, anorexia, weight loss and asthenia. The surgeon reported a subtotal resection of the stomach for carcinoma, the pathologist an "ulcerating huge lympho-sarcoma of the stomach. No involved lymph nodes found."

Points of interest in this case are mimicry, the short history, the acid values in gastric chemistry.

Mimicry led to confusion in diagnosis, and to an inclination on the part of the clinician toward a minor rather than a major malady. Periodicity in the history was not obtained, and its brevity contrasted with the usual length of that of peptic ulcer. The gastric chemistry yielded values not in concert with a duodenal ulcer. But the age of the patient and the ease of "selling" a benign lesion and a non-operative therapy produced a delay in surgery. This case is a prototype of a vast number which are treated for the lesser evil with a total disregard for probable malignancy. A survey of the histories of referred cases showed that the

physician accepted the atypical demeanor of a peptic ulcer and its classic rhythm with equal evaluation. Admittedly, there are cases of duodenal ulcer which present themselves atypically, but then we must look for some complications that distort the orthodox clinical pattern. The good old adage that it is preferable to suspect and not find than not to suspect and find too much epitomizes this case. The following is to be emphasized: where there is pre-pyloric irregularity, but not pathognomonic of a duodenal ulcer, when interpreted in terms of history, gastric chemistry and other laboratory aids, malignancy should be the tentative diagnosis until proved incorrect.

Reverting to sarcoma, while the author has encountered only two cases of sarcoma of the stomach, the following points are pertinent: 1) sarcoma tends to occur earlier in life than carcinoma, although either may occur at any age; 2) while gastric sarcoma is one of the least common of gastric neoplasms (1% of total according to Ewing's estimate) little excuse may be granted for the diagnosis of duodenal ulcer because of mimicry; 3) Mimicry, short history and gastric acid values not in concert with a duodenal ulcer would, when regarded collectively, have placed the clinician on the right track; 4) the stomach could be extensively involved with gastric symptoms of only a few weeks' duration; 5) weight loss is negligible compared to that in gastric carcinoma.

Case 4: Here two cases are illustrative of the influence of the balmy spring on the interpretation of symptoms by sympathetic physicians. A woman aged 60 presented herself during the month of May with complaints of fatigue, negligible weight loss, indifferent appetite. The physical findings were essentially negative. The only positive and sole laboratory test was a low hemoglobin. A case similar in age and clinical picture received the same "seasonal" diagnosis. The season with its soothing breezes had influenced the respective clinicians to send their patients into rural environments to enjoy early spring and remain for the summer months. Coming from medical men the advice was readily accepted. Both these patients returned in early fall with non-debatable and non-reversible pictures of gastric carcinoma. The x-ray survey merely attested to the extent of malignant involvement. One of them was operated upon, with the following reported: a round carcinoma in the posterior wall abutting upon the lesser curvature in the antrum, measuring about 5 cm. in diameter with polypoid projections along the edges and with a central flat ulceration. It is quite apparent that the marked loss of time between the onset of symptoms of malignancy and surgical intervention contributed enormously to the progress of the malady. Thus the season of the year helped lead to incorrect diagnosis. It made for an easy escape from potentialities which, at the time of their first presentation were not too informative clinically. It seems it was expected of these patients to call on their respective physicians when the leaves began to fall, to show crimson in their pallid cheeks. The diagnoses came early in the autumn, but were far from timely from the standpoint of frank symptoms of gastric carcinoma and disseminated metastasis.

Case 5 (gastric chemistry and its role in diagnosis): Whether by means of a single aspiration following a test meal or fractional aspirations and titration, evaluation of gastric chemistry aids in the assessment of activity

or inactivity of peptic ulcer. Admittedly, a normal gastric secretion does not militate against a diagnosis of gastric carcinoma, but prognostically, evidence of the presence of hydrochloric acid merits consideration. Hartman (6) referred to a statistical review of resectable gastric carcinoma which offered a possible clue to prognosis in such cases. While he declined to draw a conclusion from 80 cases, the data obtained led him to believe that "a patient with a resectable carcinoma and an acidity has a 44% chance of at least five years of life postoperatively, and twice the chance of a similar patient with free hydrochloric acid."

A male aged 31 presented himself to a very eminent physician with an over-heavy practice. The duration of his symptoms was of about seven months. The symptomatology as recited by the patient was not descriptive of a post-pyloric lesion, and on inquiry a duodenal ulcer complex was conspicuously absent. The gastric chemistry was within normal range. The duodenal bulb, while somewhat irregular in outline roentgenologically, was not conclusive for duodenal ulcer. The greater curvature, however, showed a persistent markedly serrated defect involving the distal half of the stomach. Rapid gastric clearance was evident. This case was diagnosed as duodenal ulcer. Accordingly he was administered a Sippy regimen for one year with a consequent clinical picture of malignancy. Laparotomy revealed an inoperable carcinoma of the greater curvature.

Age incidence in this case too was operative against accurate diagnosis at the onset of the dramatic picture. The low acid gastric secretion, not in concert with a duodenal ulcer were entirely ignored. Test therapy for a whole year is much too long where malignancy is lurking behind. In view of the short history, the atypical picture of a post-pyloric lesion, the low normal gastric acidity and the lack of response to ulcer therapy, the age of the patient should not have been considered as favoring a benign condition. We not infrequently encounter instances in which because of a short period of onset of symptoms, the clinician leans toward negativity. He thus ignores the fact that when a patient has been ill for a long time, the tumor, if he does harbor a neoplasm, does not seem to be progressing as rapidly or to be as highly malignant as in the case of a patient who has been ill for a brief period of time. This seeming paradox might be explained by the fact that highly malignant tumors frequently betray their existence before slowly metastasizing and less virulent tumors.

This was a case of carcinoma of the greater curvature. Re-x-ray of the stomach revealed the identical finger nail defects which had been interpreted a year before as either accentuated rugae or pressure defects from gas in the transverse colon. This interpretation was not owing to lack of knowledge but to non-application of the knowledge the clinician had. It may be emphasized here that for practical purposes it is prudent to consider lesions occurring in the greater curvature as likely to be malignant.

Case 6 (size of lesion): A woman aged 52 had had gastric disturbances for many years. However she did not relate symptoms suggestive of anatomic involvement of the gastro-duodenal region. The gastric chemistry was not particularly informing, but occult blood was intensely positive and trauma in intubation was negligible if it existed at all. The abdominal palpatory find-

ings were not significant. There was nothing in the history of sufficient substance to build up a malignant syndrome. X-ray of the stomach showed a persistent defect along the lesser curvature (12 plates comprising two different examinations a few days apart) and wall solidity was also evident. The writer advised surgery despite an unusually small plus defect on the mid-lesser curvature. This patient had canvassed an array of medical talent and in her case the veneer of neurosis was sufficiently thick to turn many an examiner of x-ray films away from considering a basic cause for the patient's vague complaints. Especially damaging were the oversentimental members of the family, but the guilt of delaying radical therapy fell on the clinicians in this case. The writer was labelled an "alarmist." This case finally reached Chevalier Jackson, Sr., of Philadelphia, who diagnosed inoperable gastric cancer, substantiated by Dr. A. A. Berg's surgical findings. The following dates speak for themselves: patient was examined June, 1936 and explored November, 1938. In the interim she was treated for chronic gastritis, which she surely had. What happened during the long time the malady progressed without recognition? Complications set in. Once clinical manifestations betrayed their existence the diagnosis of carcinoma was established beyond protest, but it was by then untimely even for palliative surgery. Harris (7) quotes McCarty's statement that "no cancer in any part of the body is early if larger than a half-centimeter in diameter." "It seems improbable," writes Harris, "that so small a carcinoma could be detected by present methods of x-ray examination of the stomach, and, likewise, it is probable that a growth of that size would be overlooked more frequently than it would be found." In this case, the defect, decidedly small, was detected early but ignored because all other essentials in the case were not recognized. Lord Berkley Moynihan makes a point refreshingly clear that there are "no symptoms pathognomonic of cancer of the stomach; the symptoms are suggestive, not conclusive." But the suggestive make for timely diagnosis, the conclusive for complications or progress beyond repair.

Case 7 (misleading roentgenologic findings, obscuring the transitional phase of a benign gastric ulcer into malignancy): This case serves as an example of a vast number of such instances. A male, aged 55, who had been diagnosed as having a gastric ulcer for 20 years, presented himself with an upper respiratory infection and aggravation of stomach symptoms. Palpatory abdominal findings were negative except for tenderness in the epigastrium. Tube tests revealed normal gastric motility and secretion, x-ray revealed a lesser curvature filling defect near the cardiac third of the stomach. The patient was hospitalized and placed on a Sippy regimen. Repeated x-ray examinations gave evidence that the ulcer had diminished in size. However, clinical improvement lagged behind. And ten weeks elapsed between first presentation with symptoms not depicting gastric carcinoma and the occurrence of a massive gastric hemorrhage followed by two succeeding hematemeses from which he died despite heroic treatment. Autopsy findings were: a gastric ulcer with malignant degeneration and metastasis to the liver and spleen.

That roentgenologic evidence of healing of a gastric ulcer does not distinguish the lesion from carcinoma stands out in bold relief in this case of ulcer-cancer. Alvarez (8) writes that some gastroenterologists "having inherited the idea that ulcers are craters and cancers are tumors, it does not occur to them that a crater may be part of a cancer. . . ." And, "It seems that the only way in which one can hope to cure cancer of the stomach is to excise it during the stage in which

it looks and behaves like a benign ulcer." As a matter of fact, despite diminution in size of the defect, the clinical picture did not parallel the roentgen evidence of healing and even the most striking clinical improvement has to be viewed with skepticism as to the ultimate outcome. It is not unusual, with hospitalization of ambulatory patients with gastric carcinoma, for there to be a favorable response to ulcer therapy. Particularly is the treatment effective when administered with adequate nursing and abundance of reassurance. One must bear in mind that as the inflammatory environment of the lesion, which contributes to the size of the filling defect and makes it larger than the actual area of carcinoma, subsides under therapy, the defect appears smaller and as apparently healing. In the absence of sustained clinical amelioration in the case under discussion, diminution should have been viewed with caution.

The implication of repair is admissible, but to conclude that repair indicates that the lesion is ulcer and not cancer is a dangerous error. A lesion of the stomach which is apparently healing as shown by roentgenologic examination may actually be malignant, and the infiltrating tissues at the base of the defect may occur while the cancer is spreading, and give the impression that the niche is filling up. Gastric malignancy, whether it be primary and ulcerated, or engrafted upon a benign ulcer, is insidiously progressive. When encountered with a long history containing some of the components of an ulcerative process, but which has changed, such as when intervals of euphoria are displaced by continuity, accentuation of symptoms, the long history may then give the false appearance of being short, and a transition from gastric ulcer to gastric cancer must be borne in mind with surgery as the safest procedure. Delay is tantamount to a summoning of death. The duration of gastric anatomic pathology is generally considered an aid in distinguishing between benignity and malignancy. A long history of years of suffering is admittedly characteristic of a simple ulcer, but when the free intervals disappear, when constancy replaces intermittency, the presumption should be that a benign ulcer has cancerated. Roentgen evidence of repair is not inconsistent with progressive malignancy. It is diagnostically advantageous to classify symptoms as vague, minor and major, and be more observant of the first two groups. Unfortunately, the accepted criteria fall into the major group of symptoms. These are late manifestations and betray the complications of gastric cancer. The writer recalls instances where excision of a presumably benign ulcer returned to surgery months later with overt carcinoma. Deductively, the lesion was primarily cancer.

The question of degeneration of a benign gastric ulcer into malignancy is still debated. The safer policy is to consider all such lesions malignant until proved otherwise. Particularly disastrous is carcinomatous metamorphosis of an ulcer in a silent area of the stomach. Added to a silent gastric chemistry and a euphoric personality, you have a well-rounded picture of a cer-

tain malignancy. The Mayo Clinic reports that malignancy was found in 10% of lesser curvature ulcers, while 65% of the pre-pyloric ulcers and all of the greater curvature ulcers were malignant. Wm. H. Stewart draws the conclusion that whereas only one lesser curve ulcer in 20 shows evidence of malignant transformation, one in every four of those situated in the pyloric canal show this change. The significance of these data for treatment of persons with ulcerative lesions of the stomach is patent.

MISCELLANEOUS ERRORS

Two cases of frank gastric cancer were treated for pernicious anemia. True, the lingual signs and histamine refractory gastric anacidity were evident. In one of the cases loss of vibratory sensation in the lower extremities was found. The pernicious anemia-like hematology led to a prolonged course of treatment for Addisonian pernicious anemia. It should be borne in mind that loss of vibratory sensation is not uncommon in the aged, and achylia gastrica is decidedly in concert with advancing age. A picture resembling that of pernicious anemia should be viewed with caution. Conner and Birkeland (9) reported the coexistence of pernicious anemia and cancer of the stomach in eleven cases. In six, pernicious anemia and gastric carcinoma apparently developed almost simultaneously, in two patients pernicious anemia followed cancer, and in three carcinoma developed after pernicious anemia. The writers argued that since both sequences occurred, each disease might conceivably predispose toward the other. That they are not antagonistic is shown by their coexistence in six patients.

It is quite apparent that difficulty might arise in distinguishing between the two from the clinical picture since both offer pictures descriptive of a malignant syndrome. When the leaning is toward pernicious anemia, and in all cases of frank pernicious anemia, a roentgenologic survey is an essential step.

A case of gastric cancer was diagnosed as a neurosis and treated accordingly for several months. On first examination, a rectal digital revealed a shelf to betray metastasis. This male aged 67, a non-complaining personality, should have been regarded as harboring a more serious malady than a neurogenesis to account for his vague gastric disturbances.

SUMMARY

This paper is a review of errors which came within my survey and which were opportunistically followed up. Browning said "Error has no end." Not few are the errors in diagnosis, but while roentgenology may be indispensable, it becomes a menace if used to avoid thinking, and when x-ray and clinical evidence are at variance, reliance should be placed on the latter. The crying need is for physicians first and always to be aware and fearful of the worst malady, and then never try and escape the cold logic of medicine by following a path of least resistance in diagnosis and treatment.

REFERENCES

1. Alvarez, Walter C.: A Study of the Histories of Forty-one Cases. *A. M. A.*, July 11, 1931, Vol. 97, No. 2.
2. Ibid.
3. Cabot, Richard C.: *Differential Diagnosis*. Third Edition, W. B. Saunders Co.
4. Carmen and Miller: *The Roentgen Diagnosis of Diseases of the Alimentary Canal*, W. B. Saunders Co., 1917.
5. Golub, Meyer: Lymphosarcoma of the Stomach with Pain-Food-Ease-Rythm of Three Months Duration. Report of Case. *The Review of Gastroenterology*, Vol. 4, No. 3, pp. 228-239, 1937.
6. Hartman, Howard R.: The Prognostic Value of Gastric An-acidity in Cases of Resectable Carcinoma. *The Jour. A. M. A.*, December 20, 1924, Vol. 83, pp. 1976 and 1977.
7. Harris, Seale: The Early Symptomatology and the Diagnosis of Gastric Cancer. Read in a symposium in the Round Table Conferences on Cancer celebrating the Fiftieth Anniversary of the Memorial Hospital, N. Y. C. (May 25), 1934.
8. Alvarez, op. cit.
9. Conner, Milton H., and Birkeland, Ivar W.: Coexistence of Pernicious Anemia and Lesions of the Gastrointestinal Tract. *Annals of Internal Med.*, Vol. 7, No. 1, July, 1933.

Clinical Evaluation of the Laboratory Tests of the Stomach

By

RUDOLF EHRLMANN, M. D.
NEW YORK, N. Y.

ROENTGENOLOGICAL examination has eliminated the necessity of many of the formerly used laboratory tests. Gastric secretion, too, can well be determined from the roentgenological findings. Gastroscopy is of importance also in the diagnosis; in the differential diagnosis, however, gastroscopy¹ often gives no more information than the Roentgen examination. None of all these methods, however, has enabled us to differentiate always clearly between an ulcerated cancer planum and a benign ulcer. The malignity or benignity of a singular pedunculated fibroma, can only be determined by microscopical examination. In cases of multiple, broadly based fibromata it is sometimes impossible to determine, even with microscopical methods, whether they are malignant or benign.

Since roentgenological methods have been predominantly used, the value of gastric analysis has been reduced considerably. Nowadays gastric analytical methods should be performed subsequent to the roentgenological examination, when additional diagnostic data seem of importance. Gastric analysis does rarely give information, if all other methods fail. One of these occasions is the aspiration of microrests.

An exact determination of acidity, by titrometric methods is hardly necessary, because de facto the secreted gastric juice has always approximately the same acidity in humans. Hyper- and hypoacidity are in reality hyper- and hyposecretion, more or less reduced in acidity by gastric mucus, reflux of pancreatic juice and bile, or emptying of the stomach and swallowing of saliva.

If, as in the case of ulcer, the quantity of gastric juice is highly increased, the reducing effect of the gastric mucus and the other above mentioned reducing factors is correspondingly low; therefore we find the gastric juice hyperacid. Besides, there is a prolonged and sometimes a continuous secretion of gastric juice. We find the picture reversed in case of atrophic gastritis, as for instance in cancer, where the small

quantity of gastric juice is easily reduced in acidity. Therefore, a titrometric determination of the acidity of gastric juice can never give exact figures. It is sufficient to have a simple estimate as to whether there is abnormally increased, normal, diminished or no secretion at all. This estimation is most easily accomplished with an indicator, as Dimethyl amido azobenzol in solution, or as a paper.

An estimation of total acidity is superfluous if a buffer-free meal or the histamin test is used. Fractional gastric analysis, which was first suggested by my coworker, M. Ehrenreich², is apparently no improvement over the single aspiration, and shows only that there is a prolonged secretion of gastric juice concurrently with hyper secretion, and this fact is self-understood.

For educational purposes fractional examination is of value, as the student is thus enabled to see for himself how the different types of food are changed in the stomach.

The following test meals are in use today:

1. Ewald Test Meal. (One roll and 200 cc. of tea)
This test meal has a distinct disadvantage, as foods are introduced into the stomach which neutralize the free hydrochloric acid. After aspiration it is impossible to detect microscopical rests, and even macroscopical rests and sometimes blood traces can not be determined.
2. Ehrmann Test Meal. (200 cc. 5-6 volume per cent alcohol)
This test meal is free from buffering effect, it increases secretion sufficiently, and it is colorless. For aspiration it is advisable to use a small gauge stomach tube with wide openings. In this way it is possible to get abnormal rests which may be contained in the stomach.

A modification of the author's method, which is in frequent use in this country, is 50 c.c. of 7% (by volume or by weight) alcohol. This method's main disadvantage is that, with the small quantity of fluid used, no real washing out of the stomach can be accomplished, and thus microrests may remain.

3. Histamin Test.

This test has the disadvantage that the injection

¹Schmieden, V., Ehrmann, R., Ehrenreich, M.: *Diagnosis of Stomach Diseases*; Mitt. Grenzgeb. Mediz & Chir., 479, 27, 1914.

²M. Ehrenreich, Fractional Gastric Analysis; Zeitschr. Klin. Med., Vol. 75, 1912.

and the entire procedure is unpleasant for the patient. Furthermore, histamin increases the secretion, even in the normal individual, to such an extent that it is almost impossible to differentiate between normal secretion and hypersecretion, caused by the presence of an ulcer. The Histamin test, however, is of importance for the determination of complete achylia due to pernicious anemia.

For practical purposes the author's test meal³ is the simplest and most convenient method. Because it is free from buffering substances, a determination of total acidity has not to be performed. The solution is transparent; thus it is possible to see the physiological color and the smallest amount of rests and cloudiness. The alcoholic solution is a sufficiently strong excitant for the gastric secretion, without being too strong, as for instance histamin. Alcohol has a certain euphoric effect on the patient which reduces the discomfort of the subsequent aspiration. The secretion of gastric juice, after the ingestion, is slightly weaker than the secretion induced after the ingestion of the Ewald Test Meal. Thus we may conclude in general that a glass of beer, which contains about 4 volume percent alcohol, provided it is not too cold, may well be tolerated by a peptic ulcer patient. Higher volume per cent alcohol induces, of course, a higher gastric secretion.

PROCEDURE

On empty stomach 200 cc. 5-6% alcohol by volume.
Alcohol USP 12 cc.
Aqua ad 200 cc.

It is possible, of course, to use white wine instead. A 200 cc. glass, or cup, is filled one-third full with white wine, which has generally 15 volume per cent alcohol, and filled up with water to 200 cc.

About one-half hour after ingestion of this solution, aspiration with a small diameter stomach tube is performed. The stomach tube should have wide openings to enable abnormal stomach contents to be evacuated. A duodenal tube cannot be used.

After the aspiration follows:

1. Inspection on
 - Odor
 - Color
 - Transparency or Cloudiness
 - Traces of Blood
 - Microrests
 - Macrorests, and other pathological findings.
2. Estimation of Secretion

Color with Dimethyl-amido azo-benzol	Estimation Value	Interpretation of the Findings
1 Deep Red	+++	Hypersecretion
2 Red	++	Normal Secretion
3 Orange	+	Normal Secretion
4 Yellow-Orange	Traces	Hyposecretion
5 Yellow	0	Achylia

In case the aspirated juice is yellow-green or green, one adds one Estimate Value (+) as in this case a part of the acid has been neutralized by the regurgitating pancreatic juice.

When the aspirated gastric content is cloudy, it indicates "insufficient cleaning" of the mucus membrane, even if the roentgenological examination does not indicate lowered motility. We have found this symptom of insufficient cleaning of the stomachal mucosa in case of hemorrhagic erosions, superficial ulcer of the mucosa, small cancer or fibromata. In case of increased secretion and stasis, findings show a specific odor of sarcina, in decreased secretion and stasis the odor of yeast and lactic acid is present. In benign stasis H₂S may be smelled occasionally. Disintegrating new growths give a definitely fetid odor.

Uffelmann's lactic acid test and the microscopic examination for lactic acid bacilli are still standard methods in the laboratory manuals. Lactic acid-forming bacilli (Boas-Opller) and lactic acid-forming cocci start to grow in case of stasis, when no, or only limited, amounts of hydrochloric acid are formed. We can detect such stasis and its causes much better by roentgenological methods and subsequent gastric analysis, than by the antiquated Uffelmann method, or by microscopical examination.

The examination on occult blood, which is important in cases of ulcerations and new growths of the intestines and the papilla Vateri, is of not too great a value, as regards diseases of the stomach.

Examination of the blood picture is always preferable, as for instance in cancer, an increasing anemia, increase of sedimentation rate, and occasional increase of the polymuclear leucocytes are very characteristic.

SUMMARY

Since Roentgenological examination has come into general use, the value of gastric analysis has been reduced considerably. Therefore, it seems to be sufficient to perform gastric analysis subsequent to Roentgenological examination, to obtain in this manner additional data. The aspirated material should be examined for quantity, odor, color, traces of blood, transparency or cloudiness, and other pathological findings. Cloudiness is indicative of microrests and "insufficient cleaning" of the stomachal mucosa. It may be present, even if the roentgenological examination does not show a decrease in motility or other abnormalities.

Titrometric methods for quantitative determination of free hydrochloric acid and total acidity give no exact figures. There is no hyper- and hypoacidity, but in reality hyper- and hyposecretion, which can be sufficiently recognized by estimation instead of determination of pseudoexact figures. The fact that hyper-, hyposecretion and achylia are typical for special diseases is the only reason for the procedure. An estimation of the gastric secretion with dimethylamidoazobenzol as indicator is sufficient. The amount of gastric secretion varies according to the various test meals used.

Ewald's test meal has the disadvantage to buffer the secreted hydrochloric acid partially and to efface the findings in regard to microrests and blood traces. The histamin test stimulates secretion to such an extent that even the normal patient may show the picture of

³Da Silva Mello, A., Ehrmann's Test Meal; Berl. Klin. Wo., No. 11, 1916.

hypersecretion. The author's test meal stimulates a sufficient secretion, is free from buffers and colorless; therefore, microrests, blood and other pathological findings can easily be observed. The modification (50 cc. 7% alcohol) is insufficient in volume to wash the stomach effectively. Pathological contents and microrests —

much more important than acidity — can therefore not be aspirated sufficiently.

Tests for lactic acid content and lactic acid-forming bacilli and cocci, and many other methods which are still included in the laboratory manuals, are nowadays antiquated and superseded.

Heredit an Important Factor for the Early Diagnosis of Gastro-Intestinal Cancer

By

RUDOLF EHRLMANN, M. D.
NEW YORK, N. Y.

A great deal of study and discussion has been devoted to the subject of peptic ulcer and its relation to the development of cancer. Such a relationship does not correspond to our experience. On the contrary, we found that the percentage of patients suffering from ulcer, who later developed carcinoma, is considerably less than the percentage of patients developing cancer in a previously healthy stomach. In particular we noted that patients with achylia inclined more to the subsequent development of carcinoma. It seems to us that a patient suffering from ulcer is rather protected against cancer, which may well be due to the hypersecretion caused by the ulcer.

Heredit, however, plays a very important role in the diagnosis of cancer of the stomach or intestines. It becomes, therefore, essential to obtain a complete history as to whether Gastro-Intestinal Cancer is, or was, present in brothers, sisters, parents, grandparents, their sisters, brothers and descendents. Careful checking of the history revealed that, in the vast majority of our cases, cancer had occurred among one or more of the above relatives. Patients, who, besides hereditary cancer predisposition, suffered from achylia, seem to be more endangered. Frequently we found that cancer among several members of a family developed at about the same age.

We, therefore, feel justified to draw the following

conclusion: If a patient complains of gastro-intestinal symptoms in whose family cancer of the gastro-intestinal tract has occurred, he should be looked upon with definite suspicion as to the possibility of the beginning development or of the presence of cancer. If the findings are absolutely negative, subsequent examination should be made in three months intervals, for at least one to one and a half years. The patient should be reminded to undergo examination immediately if the complaints re-occur. It is advisable not to postpone cursory examinations for more than three months each, as we have found that within the period of one year an inoperable cancer may have developed in the patient who did not yet show positive symptoms twelve months before.

SUMMARY

Patients with complaints, concerning the gastro-intestinal tract, where gastro-intestinal cancer occurred in the family, have always to be considered as suspicious. This is especially true if the patient suffers from achylia, or if relatives at approximately the same age are, or were, suffering from cancer, and if several cases have occurred in the family.

The findings are absolutely negative, it is of extreme importance to have the patient examined carefully within periods not exceeding three months each, for one and a half year.

OBITUARY

DR. MILLS STURTEVANT, Professor of Clinical Medicine at New York University since 1934, died at Harkness Pavilion, Presbyterian Hospital, New York City, on October 29, 1945, at the age of sixty-three.

Born in Whitefield, N. H., on April 7, 1882, he was the only son of Ira Franklin Sturtevant and Mary de Forrest Gove. The Sturtevant and Gove families were very early settlers of New England and trace their ancestry as far back as 1640.

Dr. Sturtevant received his early education in Manchester, N. H., graduating from its high school. He received Bachelor of Arts Degree from Dartmouth in

1904, and Doctor of Medicine from College of Physicians and Surgeons, Columbia University, in 1908. His association with Bellevue Hospital started with his internship on the First Medical Division, completing his houseship in 1910. From 1910-1914, he was connected with Minto Hospital, serving as Superintendent, Visiting Physician and Chairman of the Board of Trustees. He was Assisting Visiting Physician to Willard Parker Hospital from 1914-1917, and Visiting Physician to the Central and Neurological Hospital from 1917-1918. In 1918 he was appointed as Adjunct Visiting Physician to the Third Medical Division, advancing to Visiting Physician in 1927. After

serving eleven years, he became Consulting Physician in 1938. He was also Consulting Physician to the Rockaway Beach Hospital.

He was a member of the following scientific societies: American Gastro-Enterological Association, New York Gastro-Enterological Society, Societe Internationale de Gastro-Enterologie, Fellow American College of Physicians, New York Academy of Medicine, Harvey Society and Alpha Omega Alpha Society. He was a member of the University Club and a life member of Kane Lodge of Masons.

New York University appointed him instructor in Medicine in 1913, Lecturer in Medicine in 1916, Clinical Professor of Medicine in 1926, and Professor of Clinical Medicine in 1934, the chair he held at the time of his death.

Dr. Sturtevant first became interested in Gastro-Enterology when he became assistant to Dr. George Roe Lockwood, Professor of Gastro-Enterology at Columbia University. He founded the first Stomach Clinic at Bellevue Hospital. He was an excellent

teacher, and exerted a profound and enduring impression upon his students. His "Lectures on Gastro-Enterology" published by New York University in 1936 have been read extensively both by students and practitioners interested in Gastro-Enterology. Dr. Sturtevant wrote numerous papers on Gastro-Intestinal Disorders and also encouraged his associates to write. One of his most important contributions to Medical Literature was his publication with Dr. Louis L. Shapiro on the findings of Gastric and Duodenal Ulcer in 7,700 Necropsies in the Archives of Intestinal Medicine in July, 1926. He was especially interested in Peptic ulcer and his writings on this subject have appeared in the various journals. His paper on Tobacco Sensitivity in Peptic ulcer, published in July, 1936 was of particular interest to Gastro-Enterologists. At medical meetings where Gastro-Intestinal diseases were the subject, he will be remembered as a discussor who was sincere, honest, with a gracious manner and a keen sense of humor. He endeared himself both to patient and friend and in the hearts of those who knew him well he will be sadly missed.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
WM. D. BEAMER
IVAN BENNETT
J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
C. G. CLEMENTS
JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*J. J. PINCUS
B. C. HIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
J. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

* With the Armed Forces.

CLINICAL MEDICINE

STOMACH

VAUGHAN, W. W.: *Antral gastritis: roentgenologic and gastroscopic findings.* (Radiol., v. 44, p. 531, April 1945).

In antral gastritis there may be acute edematous areas of the mucosa and submucosa, ulceration of the mucosa together with the muscularis submucosa, and chronic inflammation with hypertrophy of the mucosa and round-cell infiltration of the muscularis submucosa.

Ulceration can frequently be demonstrated roentgenologically if the lumen of the antrum is sufficiently potent to allow barium to be forced through. The peristaltic waves are abnormal in that they are irregular, impaired and ineffective. The filling defect is obvious and constant.

Gastroscopic examination shows either reddening of the mucosa which is edematous and without ulcerations or a red edematous mucosa with bleeding ulcerations. Mucopurulent material is abundant. Sometimes the mucosa has a cobblestone appearance and the mucosal folds are beaded or warped; ulceration is uncommon.

Prognosis in antral gastritis is good but surgical

resection may be needed in some instances. It is essential to keep in mind that every case of antral gastritis may have possible malignant tendencies — D. A. Wocker.

BOWEL

BEALFS, P. H., AND FRANKEL, E.: *Double intussusception following multiple polyposis of the small intestine.* (Brit. J. Surg., v. 33, p. 94, July 1945).

Multiple polyposis of the small intestine is a rare condition giving rise to symptoms that are vague. Diagnosis is often missed. The patient may complain of periodic colicky abdominal pains accompanied by vomiting. Anemia, melena, and loss of weight may be found. During the pain attack an abdominal mass may be palpable: this usually is due to intussusception. Roentgenologic examination is frequently negative. The condition may suggest gall-stone, renal colic, peptic ulcer or functional dyspepsia.

A case is presented showing that neoplasm of the small intestine must be considered in the face of repeated partial or complete bowel obstruction even in the absence of demonstrable bowel lesions. — F. E. St. George.

ULCER

DONOVAN, E. J. AND SANTULLI, T. V.: *Gastric and duodenal ulcers in infancy and childhood.* (*Amer. J. Dis. Chil.*, v. 69, p. 176, March 1945).

Ulcers of the stomach and duodenum probably occur in children younger than 12 years with greater frequency than is suspected. According to the authors, ulcers have even been reported as being found in the fetus and they also are known to occur in the newborn. Up to the sixth year the diagnosis is difficult. Hemorrhage is the main finding. If the pain is epigastric and not clearly localized the suspicion of ulcers should enter the mind. Until perforation or stenosis occur the symptoms are too vague and varied to be recognized. Surgery is necessary when perforation, obstruction, repeated hemorrhage or intractable pain are present. The authors report performing a posterior gastroenterostomy on a twelve year old boy with obstruction due to duodenal ulceration. — G. Klemmer.

THERAPEUTICS

ANNEGARS, J. H. AND COWORKERS: *Use of dehydrocholic acid with arsenicals to diminish hepatitis.* (*Arch. Dermatol. Syphilol.*, v. 51, p. 112, Feb. 1945).

The decrease in liver function due to the toxic action of arsenicals was measured by determining cholic acid synthesis. The toxicity of arsenicals is greatly determined by their rate of excretion with the bile. The authors advocate doing a liver function test on all patients who are to receive arseno-therapy and believe that dehydrocholic acid administered by mouth would protect the liver from the damaging effects of the arsenic compounds. — I. M. Theoné.

SURGERY

SANDERS, R. L.: *A review of 101 subtotal gastrectomies for benign ulcer.* (*Surgery*, v. 18, pp. 229, August, 1945).

Statistical analyses of case reports in the literature show that medical treatment brings symptomatic relief to less than 50 per cent of the cases of gastric ulcer. Medical management must be continued over a long period of time and there is always the danger of the lesion being malignant or of recurring. Resection in these respects is greatly superior and also is completely or materially curative in almost 100 per cent of the cases.

Although duodenal ulcer is essentially a medical disease, about one-third of the cases still come to surgery. Palliative surgery, to a large extent, has been replaced by resection. Pyloroplasty has been abandoned and gastroenterostomy is employed only as a measure in exceptional cases. Sanders advises resection in the presence of recurrent hemorrhage, obstruction, intractable pain, and recurrent or reactivated ulcer.

Ultimate success of gastric resection depends upon its extent. The operation should include removal of

pylorus, antrum and the ulcer area. Resection of 55 to 65 per cent of the distal stomach is adequate, although some surgeons advocate resections of all the acid secreting area or more than 75 per cent of the stomach. Sanders believes this radical procedure unnecessary since it leads to nutritional disturbances.

Fifty per cent of gastric ulcers, 66 per cent of gastro-jejunal ulcers and 30 per cent of duodenal ulcers (or 30.1 per cent of all cases) had operations carried out during the past eleven years. There were 73 primary resections performed; 61 of these were for duodenal ulcer (1 death), 5 for duodenogastric ulcers (no mortality) and 7 for gastric ulcers (1 death). In twenty-eight secondary operations following failures of other operations to relieve symptoms, there was only one death. In 49 cases of primary duodenal ulcer complete relief by the operation was obtained in 33 cases, and partial relief in 10 cases. The author feels that an operative mortality of less than 5 per cent is worth noting since it is not greater than that obtained for other extensive abdominal operations. — M. H. F. Friedman.

PATH, E. J.: *Succinylsulfathiazole and phthalylsulfathiazole in surgery of colon.* (*Surgery*, v. 17, p. 773, June 1945).

Succinylsulfathiazole or sulfasuxidine and phthalylsulfathiazole or sulfathalidine are bacteriostatic to intestinal organisms when given in sufficiently high dosage. Probably the use of these drugs accounts for a great deal of the improvement in the mortality rates in colon operations seen in recent years. Preparation of the patient for operation by administration of these sulfonamides together with administration of an adequate protein and carbohydrate diet have yielded very definite benefits. Fecal fistulas do not develop and peritonitis is unknown. Hemorrhagic tendencies are not increased by the drugs. The increased safety due to use of the drugs has resulted in an increase in the incidence of single-stage operations on the bowel that are performed. However, the increased safety should not lull the surgeon into a false sense of security to result in a breakdown in the principles of good surgery. — M. H. F. Friedman.

EXPERIMENTAL MEDICINE

SECRETION

CABELLO RUZ, JULIO: *The role of the liver in bilirubin elimination.* (*Rev. Soc. Argentina Biol.*, v. 19, p. 16, 1943).

The action of the liver on the removal of the bilirubin from the plasma after an intravenous injection of this substance was studied. The liver was found to have a very important action in fixing bilirubin in rats which had undergone total or partial hepatectomy and in which 5 mg. of bilirubin had been injected. Ligation of the ductus choledochus did not affect the elimination of this substance, but a partial ligation of

the hepatic duct modified it, probably because this ligation produced a lesion in the liver. The injected bilirubin is in great part eliminated with the bile, as the diazo reaction shows. — Courtesy Biological Abstracts.

PATHOLOGY

ESCHENBRENNER, A. B.: *Induction of hepatomas in mice by repeated oral administration of chloroform.* (*J. National Cancer Inst.*, v. 5, p. 251, April 1945).

Hepatomas and cirrhosis of the liver can be induced in mice by repeated feeding of chloroform. The doses required were such as to produce necrosis of the liver. The hepatomas were histologically different from those which were produced by giving carbon tetrachloride. While no sex difference in relation to liver injury susceptibility was noted, renal necrosis occurred in males but not in females. Since the kidney necrosis was always fatal, only females were left living long enough to develop hepatomas. Doses of chloroform which were lethal within twenty four hours when given by mouth did not produce any of the anesthetic reactions which are seen when the drug is given by the respiratory route. — G. N. N. Smith.

SHAPIRO, S. AND RICHARDS, R. K.: *Prothrombin response to large doses of synthetic vitamin K in liver disease.* (*Ann. Intern. Med.*, v. 22, p. 841, May 1945).

Carbon tetrachloride was administered to dogs in order to produce liver damage. It was found that prothrombin time determined on diluted plasma (12.5 per cent) gave as good indications of liver damage as did bromsulfalein retention tests. Synthetic vitamin K was without influence on the rate of recovery after withdrawal of carbon tetrachloride. — F. X. Chockley.

DRIVER, R. L.: *Ulcer production in intestines of dogs by various enzymes under hydrostatic pressure.* (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 281, June 1945).

Driver used dogs to study ulcer production in the intestines by various enzymes under hydrostatic pressure. The author's experiments showed evidence that: (1) proteolytic enzymes, rennin, trypsin, and erepsin, under hydrostatic pressure of 90 cm. water produced necrosis of the intestines of dogs, rennin being the most active of the three, also (2) the average time required to produce a perforation with 0.1N hydrochloric acid alone was about 50 per cent more than with rennin in 0.1N hydrochloric acid, and (3) neither steapsin nor amylopsin caused necrosis under the above condition. — I. H. Dougherty.

BARONOFKY, I. & WANGENSTEEN, O. H.: *Obstruction of splenic vein increases weight of stomach and predisposes to erosion or ulcer.* (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 234, June 1945).

After carrying out experiments on rabbits and dogs the authors concluded the following: (1) Partial ob-

struction to the venous outflow from the stomach increases its weight in both rabbits and dogs. (2) Esophageal varices can be produced by portal or splenic vein obstruction and, when histamine-in-beeswax is given to such animals, esophageal and gastric erosions and bleeding are produced. (3) Portal or splenic vein obstruction abets the ulcer diathesis. — I. H. Dougherty.

BARONOFKY, I., LANNIN, B. G., SANCHEZ-PAZ, MERA, E., AND WANGENSTEEN, O. H.: *Billroth I gastric resection: Extent necessary to protect against histamine-provoked ulcer.* (*Proc. Soc. Exp. Biol. Med.* v. 59, p. 229, June 1945).

The above authors investigated the extent of gastric resection necessary to protect against histamine-provoked ulcers using the Billroth I method. Their results led to the conclusion that small gastric resections (25 and 50 per cent) in dogs, when accompanied by an afferent loop (Billroth I), are accompanied by a high incidence of histamine-invoked stomal ulcers. When a three-quarter gastric resection (75 per cent) is done, however, stomal ulcers cannot be produced with histamine. Their experiments suggest that it is unlikely that substitution of the Billroth I for the Billroth II plan of operation, in which a short afferent duodenal loop is employed, will protect against recurrent ulcer with less sacrifice of stomach. A three-quarter resection will protect against the histamine-in-beeswax provoked ulcer, whether the operation is carried out on the Billroth I or II plan of operation. — I. H. Dougherty.

PATHOLOGICAL CHEMISTRY

GREGORY, R., EWING, P. L., AND LEVINE, H.: *Azotemia associated with gastrointestinal hemorrhage.* (*Arch. Intern. Med.*, v. 75, p. 381, 1945).

The influence of various procedures on the extent of azotemia due to gastrointestinal hemorrhage was studied in dogs. Lowering of the blood pressure by bleeding resulted in rises in blood-urea nitrogen to 25 to 40 mg. per 100 ml. Blood given by stomach tube raised blood urea nitrogen to 25 to 30 mg. per 100 ml. Anemia to quite extensive degrees had no influence in the alimentary azotemia. A decrease in renal function following low blood pressure or dehydration may produce azotemia as can also the absorption of digested blood proteins. — F. X. Chockley.

METABOLISM and NUTRITION

HAMILTON, J. W.: *Nutritional requirements of rabbits, guinea pigs and hamsters.* (129p. Thesis: Univ. Mich., 1943).

On simplified diet containing dextrin 30, casein 20, cellulose 15, lard 11, salts 4, brewer's yeast 15 and corn starch 5, fortified with vitamins A, D and E (also C for guinea pigs), rabbits and guinea pigs grew normally but the diet was not adequate for reproduc-

tion. Every young guinea pig and most of the young rabbits had generalized extensive hemorrhages. When 0.005% of 2-methyl-1,4-naphthoquinone was included in the diet weaning percentage was reasonably good and the incidence of hemorrhages was negligible. Neither soybean nor wheat germ oil is a reliable source of vitamin K. A phytol concentrate and pure phytol increased the weaning percentage and reduced the incidence of hemorrhage. Dried yeast contains all the water-soluble vitamins required by these species for growth and reproduction and they are extractable with hot water. Considerable extraneous material is precipitated by adding alcohol to a concentration of 50%. Guinea pigs grow at a normal rate if 2% of the 50% alcohol-soluble material is included in their diets. An aqueous extract of liver is also an excellent source of the unrecognized vitamins required by these animals. Hamsters grow normally on a ration of casein 20, dextrose 65, lard 8, cellulose 3 and salts 4, supplemented with vitamins A, D, E, K, thiamine, riboflavin, pyridoxine and pantothenic acid; if nicotinic acid, choline and inositol are added, this ration is adequate for reproduction. If inositol is omitted they bear shapeless, decomposed and bloody embryos. If nicotinic acid or choline, or both, are omitted the weaning percentage is reduced. On a vitamin E-deficient ration they grow slowly, the deficiency becomes acute in four to sixteen weeks and they collapse suddenly and die. Administration of α -tocopherol shortly after collapse may produce spectacular recovery. On a vitamin K-deficient diet hamsters continue to grow for four to six weeks, remain stationary or decline in weight for two to three weeks, and then resume growth and attain normal mature weights. Examination disclosed hemorrhagic areas during the period of arrested growth. If vitamins E and K are omitted they grow slowly, collapse and die after five to seven weeks, and are severely hemorrhagic. Three generations have been reared on simplified diets which contain none but the recognized vitamins. — Courtesy Biological Abstracts.

SAUNDERS, J. C.: *Food rationing and supply*. (Lancet, v. 247, p. 580, 1944).

The enormous increase in rickets cannot be due to the institution of a whole meal loaf of bread unfortified with calcium, but is in fact due to the cessation of imports of cod-liver oil and other anti-rachitic preparations. — Courtesy Biological Abstracts.

EMERSON, G. A. AND OBERMEYER, H. G.: *Non-availability of fecal thiamine in thiamine deficiency*. (Proc. Soc. Exp. Biol. Med., v. 59, p. 299, June 1945)

From the results of a number of experiments the authors concluded that rats maintained on a thiamine-deficient diet excreted essentially the same concentration of thiamine in their stools as did animals receiving 5 or 50 micrograms of thiamine daily. The output of feces was greatly reduced in the thiamine low group.

During the later stages of the depletion the thiamine was present largely in the form of cocarboxylase.

The fecal thiamine of the thiamine deficient rats was not available when administered curatively by the oral route to animals which had levelled-off in weight on a thiamine-low diet. — I. H. Dougherty.

MITCHELL, H. H.: *Adaptation to undernutrition*. (J. Am. Dietetic Assoc., v. 20, p. 511, 1944).

Experience and history indicate the ability of the animal body to adapt itself to inadequate supply of one or more essential nutrients in order to minimize the effects of deprivation, whether of total food, protein, calcium or of some of the vitamins. There is no proof that the body can adapt itself to any diminution, however low, or that any two persons have the same ability.—Courtesy of Biological Abstracts.

DAVIS, J. E. AND GROSS, J. B.: *Hemolytic anemia produced by the feeding of fat and choline*. (Am. J. Physiol., v. 144, p. 444, August 1945).

Dogs, on a normal diet and having a normal blood count were given two doses each of 60 grams of fat and 10 mgms. of choline per kilogram body weight. This was followed by reduction of the erythrocyte count by 20 to 30 per cent. The anemia was accompanied by a significant increase in the icterus index. Essentially the same results were obtained on human subjects. The supposed mechanism is that the excess fatty acids not resynthesized to neutral fat escaped as such, while choline increasing the blood and oxygen supply to the bone marrow acted as a brake on the compensatory activity of the bone marrow. —W. J. Snape.

RICHTER, C. P.: *Nutritive value of dextri-maltose determined by the single-food choice method*. (Proc. Soc. Exp. Biol. Med., v. 59, p. 260, June 1945).

The single-food choice method has been used in previous studies to determine the nutritive value of dextrose, sucrose, casein, and other substances, together with the effect produced on their utilization by thiamine hydrochloride. This method has now been applied to the study of the nutritive value of dextri-maltose.

Twelve female rats kept on a diet in which dextri-maltose constituted the sole source of nourishment survived on the average of 85 days. These rats lived 48 days longer than rats of the same weight kept on a single food diet of dextrose or sucrose; and 11 days longer than rats kept on dextrose with access to the 0.02 per cent solution of thiamine hydrochloride.

Their food intake was higher and they lost weight at a slower rate than the dextrose and thiamine fed rats. Their activity, water intake and vaginal smears were essentially the same. It was concluded that the dextri-maltose contains sufficient amounts of thiamine to utilize to its fullest the available carbohydrate.—I. H. Dougherty.

IVANOVA-GLUKHOVA.: *Capillary microscopy and venous pressure in scorbutic and dystrophic children.* (*Pediatrics (Moscow)*, v. 1944, p. 31, 1944).

Microscopic examination of the nail bed capillaries was performed in 62 cases of scurvy. The changes found appeared to correspond with degree of alimentary dystrophy accompanying the scurvy. In cases with either no dystrophy or with mild dystrophy, the capillaries were either normal with some extravasates, or they exhibited archlike loops with both branches, especially the venous, dilated. Cases with severe dystrophy showed tortuous or candelabrum-like capillary loops. In the presence of hunger edema marked ramification of the loops was seen. These changes were found both in severe cases of scurvy, and in mild cases of scurvy with severe dystrophy. In uncomplicated cases of scurvy, the capillaries were seen to return to normal upon recovery; in cases complicated by edema the changes persisted for a long time after recovery. The venous pressure was measured in 25 children between the four ages of one to nine years. It was found to be normal in uncomplicated cases, in cases with edema low pressure was noted. Five cases are reported and the findings discussed. The literature is reviewed.—Courtesy of Biological Abstracts.

HEITMAN, HUBERT JR.: *Vitamin deficiencies in rations of natural foodstuffs.* (81p. Thesis: Univ. Missouri, 1943).

Approximately forty per cent of the pigs born alive in the corn belt die before they are old enough to wean even when the rations of the mothers are adequate according to current feeding standards. As shown heretofore, these standards are faulty; most of the mortalities are due to nutritional deficiencies, the most important probably being one or more unrecognized vitamins. These deficiencies were studied with the rat. Rats on a commonly used swine ration supplemented with casein grew at about 80 per cent of the normal rate but eventually attained normal mature weights. Paired feeding trials with weanling rats showed that some combination of thiamine, riboflavin, pyridoxine and pantothenic acid increased the growth rate to normal and was as effective as was a supplement of all 14 known vitamins. None of the 4 was effective alone. The ration supported normal reproduction through parturition; the young were normal at birth but only 16.5 to 63 per cent were weaned at 28 days of age, and the weaning weights were subnormal. The only characteristic symptom was a lethargic condition preceding death. Moderately fatty livers (prevented by choline) were found at autopsy, and a few cases of hemorrhage. No acetone bodies were detected in the urine, there was no anemia, the whole blood clotting time and the prothrombin time seemed normal. Addition of choline to the basal ration increased the weaning percentage but not the rate of growth whereas further addition of all other known vitamins did not increase weaning percentage. The addition of thiamine,

riboflavin, pyridoxine and pantothenic acid, with or without choline, increased the rate of growth of the litters to normal. Addition of all other known vitamins had no further effect. Supplements of dried liver or of aqueous or alcoholic extracts increased the survival rate to normal and sustained normal growth; the accelerated growth rate is attributed to the four vitamins mentioned, the effect on litter survival to the presence of an unrecognized factor which is adsorbed on fuller's earth at a pH of 1. A folic acid concentrate was an excellent source and folic acid may be related to it or identical with it. Differences in the nature of the deficiencies before and after weaning may be related to symbiotic microbial synthesis in the alimentary canal.—Courtesy of Biological Abstracts.

MISCELLANEOUS

MARSHAK, A. AND BYRON, R. L., JR.: *The use of regenerating liver as a method of assay.* (*Proc. Soc. Exp. Biol. Med.*, v. 59, p. 200, June 1945).

One of the authors had previously described a technique for obtaining free nuclei. By applying this method a procedure for assay has been developed by means of which it has been possible to test many substances each week in order to study the rate of mitosis in regenerating liver.

The authors came to the following conclusions: (1) The time at which mitosis in regenerating liver reaches a maximum varies with the age of the animal. (2) P^{32} uptake by regenerating liver, three hours after intravenous administration of labelled disodium phosphate, varies with time after partial hepatectomy. This variation may be related to changes in liver volume or to mitotic activity or both. (3) P^{32} retention 27 hours after subcutaneous administration of labelled disodium phosphate, shows little variation with time after operation. (4) The mitotic rate provides a useful index which may be used in assaying the effect of various agents on the reproduction of liver cells. — I. H. Dougherty.

GOMORI, G.: *The microtechnical demonstration of sites of lipase activity.* (*Proc. Soc. Exp. Biol. Med.*, v. 58, p. 362, April 1945).

A microtechnical method for the demonstration of the presence of lipase in paraffin sections of tissues is described. The substrate acted upon by the lipase is either a palmitic or stearic ester of hexitans in which most of the hydroxyl groups are etherified. These are available commercially. By the technique described here, Gomori found lipase in liver, pancreas, lung, adrenal, stomach and small intestine. In the pancreas the lipase is found only in the region where zymogen granules are present: it is absent from islet cells. No lipase was demonstrated in the spleen, lymph nodes, brain and muscle. — M. H. F. Friedman.

HODGSON, C. H.: *Typhoid and paratyphoid fever: experience with 84 cases.* (Proc. Staff Meet. Mayo Clinic, v. 20, p. 257, July 1945).

The author studied the 84 cases of typhoid and paratyphoid fever in the British-American Hospital in Lima, Peru. Each patient seemed to present his own problems. Ten of the cases were diagnosed as paratyphoid, 71 as typhoid and 2 as a mixed infection. An additional 25 to 30 cases had clinical evidence of typhoid fever but lacked laboratory proof.

Complications are what make typhoid a dangerous disease. Hemorrhage is the most common gastrointestinal complication. The tendency to hemorrhage is not related to the severity of the disease and is unpredictable. Other complications seen in these patients were intestinal perforation with peritonitis, hepatitis with jaundice, and acute cholecystitis (which may become chronic). Five deaths resulted in the 84 cases (6 per cent). The causes of death were 1) toxemia and dehydration, 2) intestinal perforation, hemorrhage and peritonitis, 3) lobar pneumonia and pericarditis.

Sulfaguanidine is no longer used in treatment since it does not affect the course of the disease nor reverse a positive stool culture to negative. High vitamin low residue diet is necessary. Vitamin administered parenterally may be indicated. Dehydration must be overcome: 3 to 4 litres of fluid daily must be given. Salt lost in perspiration should be replaced. Blood transfusions may be needed. Sulfonamides and penicillin in treatment of secondary complications, such as peritonitis, may be used with good results.—F. N. Chockley.

CARMICHAEL, E. B., STRICKLAND, J. T. AND DRIVER, R. L.: *The contents of the stomach, small intestine, cecum and colon of normal and fasting rabbits.* (Amer. J. Physiol., v. 143, p. 502, April 1945).

The contents of various organs of the digestive system of the rabbit were removed, weighed, and dried to constant weight. The rabbits were all kept on liberal diets prior to the beginning of the experiment. The animals were sacrificed either after periods of fasting with muzzles or after fasting without muzzles. Normal controls consisted of animals that had not been fasted at all.

Within 24 hours after commencement of the fast the stomach contents dropped to about 50 per cent of the normal values. Within a few days of fasting only water and some hairs or very small quantities of food were found in the stomach.

The contents of the small intestine decreased during fasting but the viscosity and appearance seemed fairly constant. Muzzling appeared to exert no influence on the amount of dry residue from the intestine.

The cecum acted as a reservoir for food and was filled even after the stomach had been emptied by the

fasting process. The colon tended to become empty fairly rapidly during the first two days of fasting. Subsequent fasting produced little change in the dry content of the colon.—M. H. F. Friedman.

SUMNER, J. B. AND NYMAN, M.: *The oxidation of bilirubin by peroxidase.* (Science, v. 102, p. 209, August 24, 1945).

It has been assumed that hemoglobin is broken down to biliverdin and this is ultimately reduced to bilirubin. Although this may occur, it is also possible to convert bilirubin to biliverdin in the liver by means of peroxidase. Catalase inhibits this reaction probably through destruction of hydrogen peroxide.

KRANTZ, J. C. JR., KIBLER, D. V. AND BELL, F. K.: *The neutralization of gastric acidity with basic aluminum aminoacetate.* (J. Pharmacol. Exp. Therap., v. 82, p. 247, 1944).

A new compound, the basic aluminum salt of aminoacetic acid, has been prepared. Its capacity to buffer and neutralize hydrochloric acid has been studied. Its prompt and prolonged buffering of acid bespeaks the use of the compound in the treatment of hyperacidity and peptic ulcer. On the basis of the aluminum content, basic aluminum aminoacetate is 42 per cent more efficient in acid-consuming power than dried aluminum hydroxide gel. Certain theoretical considerations of its use have been discussed. Feeding studies on rats and preliminary clinical trials as an antacid in man are recorded.—Courtesy of Biological Abstracts.

LIFSON, N., LORBER, V. AND WOOD, H. G.: *Position of carboxyl carbon of fed acetic acid in glucose from rat liver glycogen.* (Fed. Proceed., v. 4, p. 47, March 1945).

After feeding glucose and carboxyl labelled radioactive sodium acetate to fasted rats, radioactive carbon was found in the liver glycogen. The conclusion was that it was due to CO₂ fixation alone.

It became of interest to determine whether the positions of heavy carbon of liver glucose after carboxyl labelled acetate feeding are the same as after administration of labelled sodium bicarbonate. Fasted rats were fed by stomach tube glucose and sodium acetate with excess carbon in the carboxyl groups of the latter. Two or three hours later the extirpated livers showed a detectable excess of C¹³ present only in carbon atoms 3 and 4 of the glucose, just as for CO₂ fixation. These results are consistent with exclusive incorporation of the heavy carbon into the glycogen by CO₂ fixation.—I. H. Dougherty.

Army Exceeds Quota on Release of Doctors

The Army's quota of 13,000 doctors to be released to civilian life by December 31 has been exceeded six weeks in advance of the deadline, Major General Norman T. Kirk, Surgeon General of the Army, has announced.

The total number of doctors who have been separated from the service reached 13,320 for the week ending November 16. For the same week the total for nurses who have been retired came to 20,222 and the dentists' total was 2,460, according to General Kirk.

Even though the December 31 quota has been attained sooner than expected, Medical Department officials pointed out there will be no slackening in the Army's efforts to return as many doctors to civilian life as possible in the quickest time.

From a peak strength of over 45,000 doctors, General Kirk has announced that all but 11,000 will be out of the service by the first of June. In order to do this the Army must continue to follow its policy of expediting the release of doctors as well as other Medical Department personnel in every way possible.

Gen. Kirk Presents Awards at Walter Reed Hospital Ceremonies

Major General Norman T. Kirk, The Surgeon General of the Army, awarded Distinguished Service Medals to Major General Shelley U. Marietta, Commanding General of Walter Reed General Hospital, Brigadier General James S. Simmons, Chief Preventive Medicine Service, and Brigadier General Edward Reynolds, Chief Supply Service of the Army Medical Department, at the regular monthly meeting of officers of the Medical Department at Walter Reed General Hospital.

The Bronze Star Medal was also presented to Lt. Colonel Louis F. Williams of the Pharmacy Corps and eight Legions of Merit were also awarded during the same ceremonies to members of the Medical Department who have distinguished

themselves by outstanding performance of duty.

General Marietta's citation stated that as Commanding General of Walter Reed General Hospital as well as the Army Medical Center and as Commandant of the Medical Department Professional Service Schools from December 1939 to August 1945, he "displayed outstanding leadership and administrative and professional ability of a high order in discharging his highly responsible duties."

"He organized and trained Medical Department units and personnel in medico-military activities," the citation read, "while at the same time carrying out his responsibilities for the proper performance of the many-times expanded missions of the Army Medical School, the Enlisted Technicians School, the Army Dental School, the Army Veterinary School and the Walter Reed General Hospital."

"Under his guidance the Army's wide needs for blood plasma and both the Army and Navy needs for immunizing biologics were always fulfilled. He helped pioneer numerous innovations for the care and treatment of the sick. General Marietta's contribution to the war effort, made possible by the diligent application of his exceptional talents, was an important one and reflects highest credit upon himself and the military service."

General Simmons' citation said, "the service he organized and developed carried out a world-wide program of military and civil public health which secured both immediate and enduring benefits by reducing hazards to the health of the troops, civilians engaged in essential war work, and refugees and displaced persons."

"By applying the best available knowledge and fostering research, he developed and extended new information on the causes and prevention of communicable diseases, on the improvement of nutrition for soldiers and on the reduction or elimination of the health hazards of mechanized warfare and industrial occupations. His teachings, influence of personality and adherence to ideals, inspired and established a

positive concept of health for troops and civilians.

"With extraordinary foresight, he was in advance of events, devising measures for health protection before critical needs arose; and with dynamic energy he overcame severe difficulties. By protecting the health of the Army and conserving the health of the nation, General Simmons contributed directly to winning the war."

General Simmons serves as Chief of Preventive Medicine Service for the Surgeon General's Office.

General Reynolds implemented a program "insuring the timely and adequate flow of medical supplies to all parts of the world, and effected changes in the organization and functions of district and depot procurement agencies that resulted in increased operating efficiency and material savings in trained manpower."

"Under his control," the citation continued, "both the procurement and distribution of supplies many items of which were difficult to produce and yet of vital necessity to the troops, proceeded smoothly. General Reynolds, by his exceptional leadership and administrative ability, contributed greatly to the successful accomplishment of the Medical Department's mission of providing the finest possible care and treatment for the sick and wounded."

General Kirk also awarded the Legion of Merit to the following members of the Office of The Surgeon General: Colonel Floyd L. Wergeland, MC, Director Training Division; Colonel Bryan C. Fenton MC, Director Special Planning Division; Colonel Robert E. Peyton MC, Director Mobilization and Overseas Operations; Colonel Joseph F. Crosby, VC, Chief Policies Branch and Assistant Director of Veterinary Division; Lt. Colonel Mason Ladd, Director Legal Division; Lt. Colonel Aims C. McGuinness, MC, Assistant Administrator of Army Epidemiology Board; Lt. Colonel Thomas H. Sternberg, MC, Director Venereal Disease Control Division, and Lt. Colonel Lee I. Park, Director of the Renegotiation Division.

Carcinogenic Value of Oxidated Oils

Sun-flower Oil

By

PROF. ANGEL H. ROFFO

BUENOS AIRES, ARGENTINA

IN 1938 I already reported the experimental results obtained by feeding rats with fats and oils oxidated by heating, experiments which resulted in the production of malignant tumors, most of which were localized in the stomach although some of them were also found in the liver. During this investigation the animals were fed on their ordinary diet of bread and milk to which fats and oils were added in tolerable doses.

The lesions induced in the stomach, both in the malpighian and in the glandular zone, appeared regularly under the same form, and their evolution included different stages which may be summarized in three periods: first, the forming of necrotic and hemorrhagic ulcerations which in a second stage acquire the type of the round ulcer, with outjutting and infiltrative edges, and finally the cancerization in form of ulcerative or vegetative tumors with the histological structure of the pavement carcinoma and of the adenocarcinoma.

The carcinogenic action of these fats was related to their content in sterols and their derivatives, as a result of the oxidation brought about by heating them at the high temperatures necessary to boil these fats. This has been confirmed by the chemical and spectrographical determinations carried out in the Institute and which were demonstrative both of the production of polycyclic hydrocarbons and of the oxidation process.

On the other hand, this research work confirms the role played by the cholesterol derivatives in the cancerization process as it demonstrates that the cholesterol which has been oxidated by heating or by the action of ultra-violet rays, undergoes physico-chemical and biological changes which confer to it the value of a carcinogenic agent since its ingestion induces cancerous lesions in the stomach (1) (2).

During the elemental analyses effected with unheated and heated cholesterol, it was observed that the theoretical formula of cholesterol $C^{27}H^{46}O$ is transformed into $C^{27}H^{46}O^3$ when heated or submitted to the oxidating action of ultra-violet rays. That is to say, the modifications undergone by this substance are characterized by an oxidation process in the lateral chain and by an esterification of the tetracyclic nucleus. These modifications may be better estimated in the following summary:

	Non-irradiated Cholesterol	Irradiated Cholesterol
	Per Cent	
Carbon	83.936	75.00
Oxygen	4.148	14.29

Hydrogen	11.916	10.71
Formula	$C^{27}H^{46}O$	$C^{27}H^{46}O^3$

This oxidation process is produced in a similar way in boiled fats. We may observe, for instance, that in anhydrous cow fat, the boiling temperature of which is 350° , there is an increase in oxygen. This fact is important as it confirms the oxidation process and as it was in this form that the fat was incorporated to the diet of the experimental animals.

Average of 18 elemental analyses of cow fat, unheated and heated for 1 hour at 350° C.

	Carbon	Hydrogen	Oxygen
	Per Cent		
Cow fat	63.12	12.38	24.50
Boiled cow fat	62.10	12.71	25.19

Now, fats and oils contain a considerable amount of cholesterol, together with 3 glycerides, the tripalmitine, the tripalmitine and the tristerine, substances which are important for determining the fusion. The interesting feature for us is the presence of cholesterol which is found in fats, as indicated previously, in a proportion of about 0.50%. On heating them at boiling temperature, this substance is totally oxidated, converting itself into a derivative which does not precipitate with digitonin.

Determination of Cholesterol in Fats (Digitonin Method)

	Previous to heating			After heating at 350° C		
	Total gr.-%	Free gr.-%	Compound gr.-%	Total	Free	Compound
Cow	0.450	0.379	0.071	0	0	0
Pork	0.435	0.204	0.230	0	0	0
Sheep	0.480	0.305	0.175	0	0	0

The changes in the amount of cholesterol contained in heated fats, and the structural modifications on account of which it does not precipitate with digitonin, are a clear evidence that during the heating process an intense chemical modification is produced which, according to our knowledge of its molecular structure, must modify the oxydril group of ring A without which the forming of digitonide cholesterol is not possible.

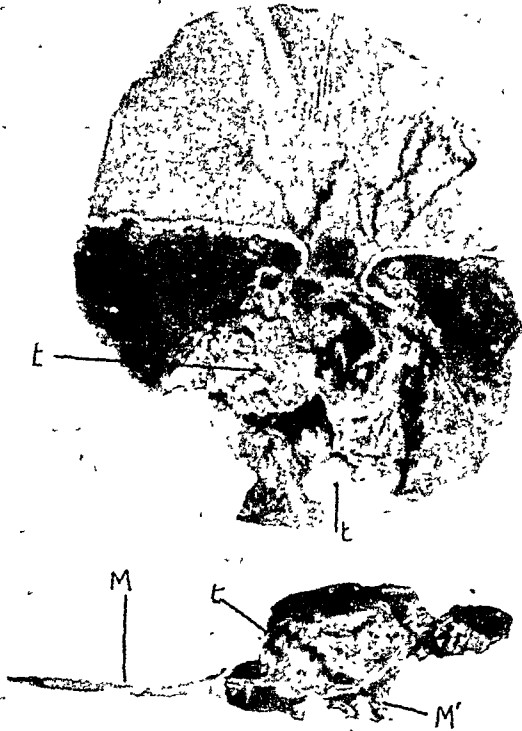
Experiments with Sun-Flower Oil

The experimentation reported herein was undertaken with sun-flower oil (*Heliantus annus L.*) as a complementary study to the one previously carried out with olive oil (*Oleo Sativa Europca*) (4).

It is well known that these oils are formed by a mixture of glycerides, as palmitic, stearic, linoleic and arachidic acids, which in some instances make up 90%

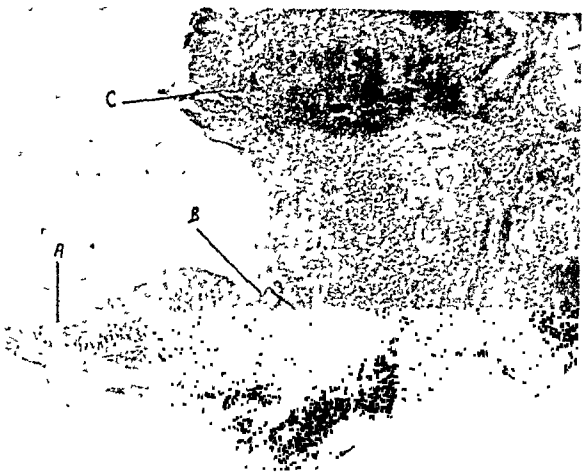
of the components. They contain moreover phytin, pigments, unsaponifiable vitamins and small amounts of esters and fatty acids which confer to it its characteristic odor. This composition varies from one oil to another, some of the components prevailing upon the others according to the different oils. Thus, although the oleic acid prevails in olive-oils in a proportion of 84% it is only 33.4% in sun-flower oils, whereas the linoleic acid which in olive-oils only ranges from 4-7% amounts in sun-flower oils to 57.4%. These differences are best appreciated in the following summary of Jamieson and Boughman:

These last substances are the most interesting ones as among their components, the phytosterols are similar in their structure to the polycyclic hydrocarbons which, according to the determinations performed in the Institute, were present in the oils used in these experiments in a proportion of 1:76 in the olive-oil and 2:23% in the sun-flower oil.

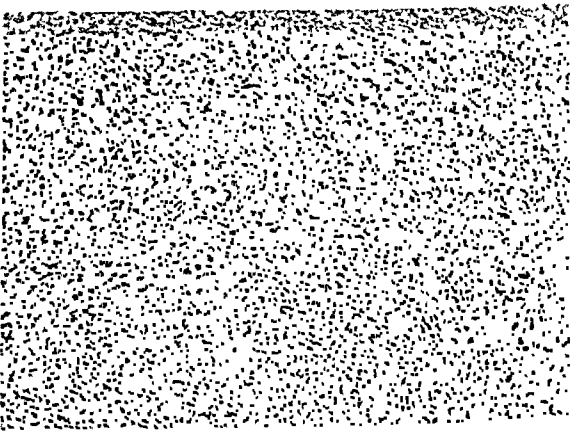


Photograph 1 — Stomach of rat 6602-11. Enormous vegetative tumor which extends itself through the whole glandular zone, from the epithelial folding to the pylorus -t-.

Photograph 1 bis — Supero-inferior section of the tumor of the foregoing stomach. M - mucosa of the stomach, malpighian zone. T - tumoral mass with invasion and growth in the external mucosa - M'.



Microphotograph 1 — Fusocellular sarcoma of the foregoing stomach. In -A- rests of the gastric mucosa. In -B- ground of the old ulceration. In -C- enormous sarcomatous mass of the fusocellular type with peritoneal invasion.



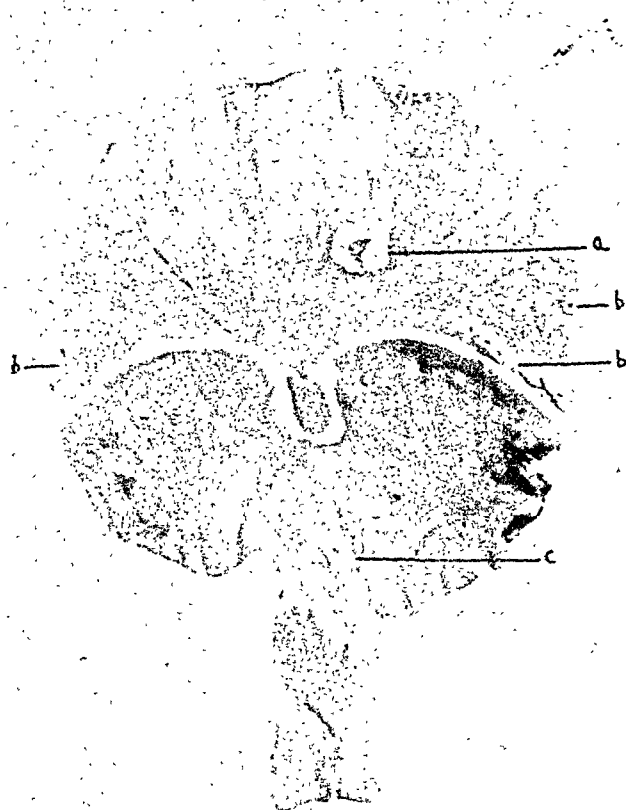
Microphotograph 2 — Higher magnification of the section of the foregoing tumor, where the spindle-cell structure may be observed.

Composition of the olive-oil and of the sun-flower oil,
per cent

	Olive-oil	Sun-flower Oil
Oleic acid	84	33.4
Palmitic acid	6,9—9,4	3,5
Linoleic acid	4 —7	57,4
Stearic acid	1,4—2,3	2,9
Arachidic acid	0,2	0,6
Unsaponifiable substances	1	1,2
Lignoceric acid	—	0,4

Actual Experimentation

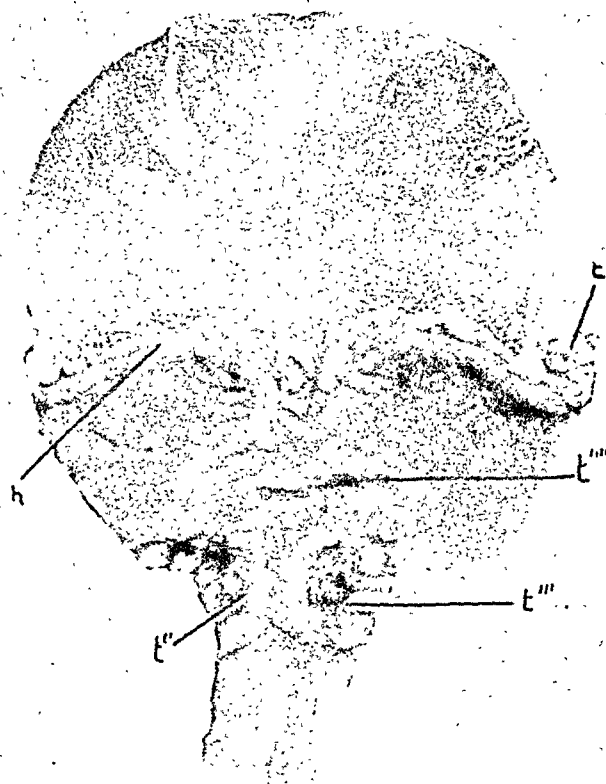
The present investigation is concerned with the study of the sun-flower oil and may be considered, on account of the lesions produced, as complementary to the previous report on olive-oil. In both these experiments a great similitude in the evolution and in the anatomo-pathology of the process was observed. The actual study involves two series of 100 white rats which were fed with their ordinary soup of milk, bread and bran. In each meal small doses of 1 cc. per



Photograph 2 — Stomach of rat 6602-17. Multiple tumors developed in the malpighian zone and in the glandular zone. In -a- tumor of the type of the pearled pavement carcinoma. In -b- round ulcers with papillomatous edges. In -c- round ulcers with infiltrated edges in the prepyloric zone (adenocarcinoma).

capita and per day of boiled sun-flower oil were added. Young animals 2-3 months of age were selected.

During the first months they did not present any trouble and, on the contrary, their general condition



Photograph 3 — Stomach of rat 6602-71. Multiple tumors developed in the malpighian zone -t, h- and in the glandular zone -t', t'', t'''-

This study was begun on March 10, 1942 and was ended on November 5, 1943; during this period numerous lesions were induced in the stomach of 60 animals, lesions which responded to the same evolutive process and which developed as follows: 1st, simple



Microphotograph 3 — Microphotograph of the stomach of rat 6602-17. Carcinoma of the malpighian zone.

and their weight improved. It is only after 6 months that a declination of health was observed together with loss of appetite and a consecutive loss of weight. Mortality in these animals began to be observed after the 6th month of the new diet, although the greatest number of deaths occurred after a period of 12 months, when the old age, and with it the cancer age of rats begins.

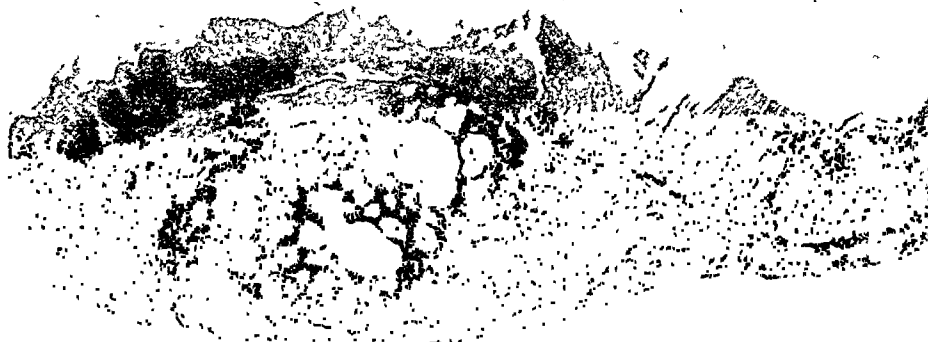
ulcer; 2nd, round ulcer and 3rd, cancerization. These lesions are multiple, only very few animals having a single gastric ulceration.

In the following tables the lesions found during the post mortem examinations of the animals are summarized; most of these lesions involved both zones of the gastric mucosa of these gnawers.

It should be recalled in order to better evaluate this

process that the mucosa of the stomach of rats is similar to that of the solipedes, i. e., it is formed by two zones: the first one, corresponding to the upper half, has the structure of the malpighian mucosa and

Moreover, I have pointed to the connections existing between the numerous carcinogenic agents which have been discovered by different authors and which possess, all of them, the central phenanthren nucleus of chol-



Microphotograph 4—Section of the tumor -r- of the foregoing stomach. Histological type of the pearled pavement carcinoma.

may be considered as an expansion of the œsophagus. The other one, corresponding to the lower half is the glandular one and therefore the true gastric mucosa. Both zones are separated by an epithelial folding. For

esterol. It is through the disintegration of the molecule of this substance by the action of heat or any other oxidating matter that the carcinogenic polycyclic hydrocarbons, preferably an oxysterol, are formed.



Microphotograph 5—Histological cut section of tumor -r'''- of the same stomach. In -U- ground of the primitive ulceration. In -T- adenocarcinomatous tumors developed in the edges of the ulceration.

more details, readers are remitted to Bulletin No. 48, 1938, page 407, where I already reported a detailed comment.

This multiple histologic structure is important from the cancerologic point of view as it has served to confirm that the action of the carcinogenic agent is exerted both in the malpighian and in the glandular zone and also in the epithelial zone of separation, inducing multiple lesions. The conjunctive submucous tissue may also be attained as evidenced by rat 6602-11 which developed an enormous sarcoma of the stomach.

Interpretation of the Process

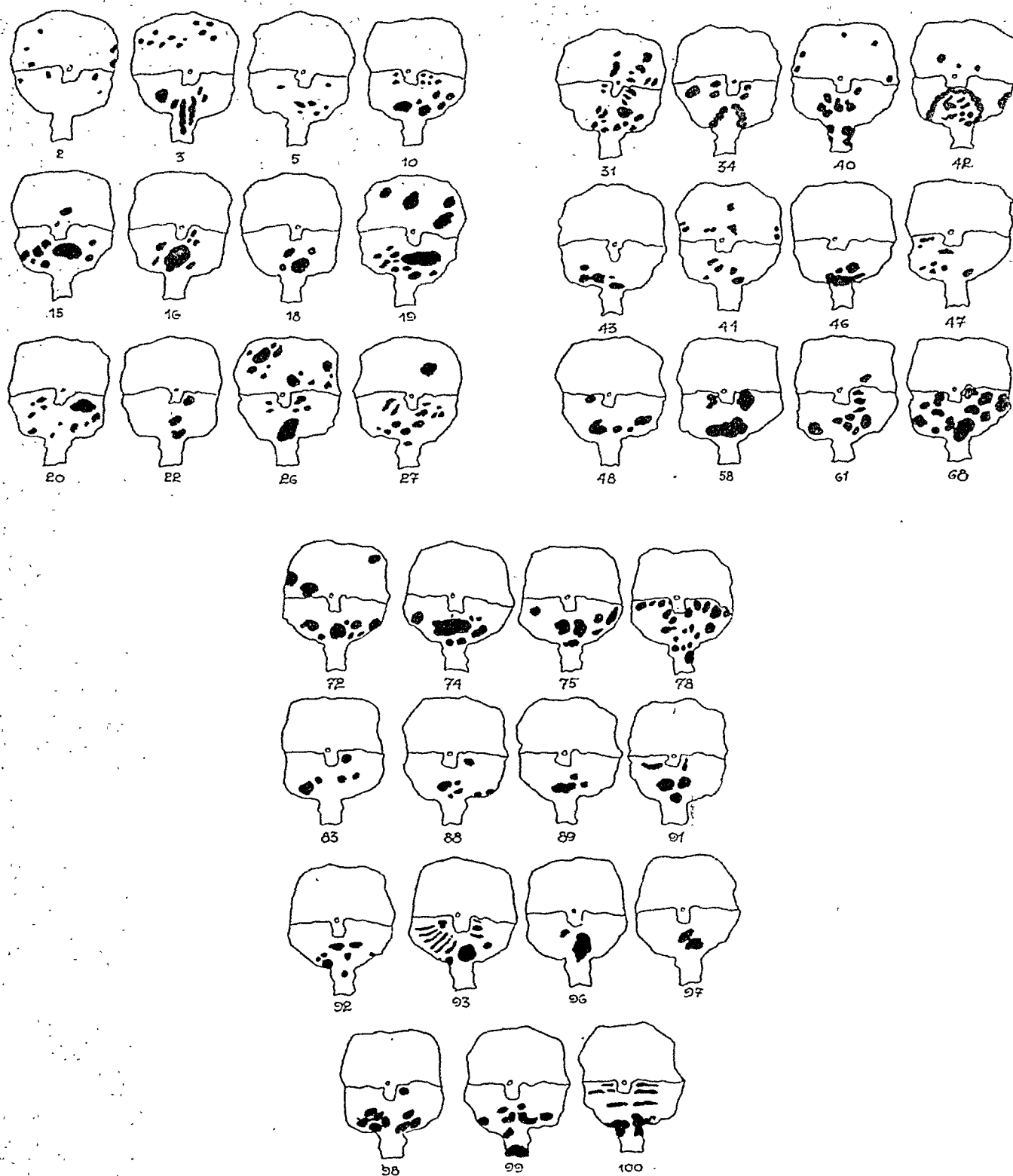
On interpreting this process of cancerization, we come to the same conclusions as in the experiments with pure olive-oil and animal fats, when I ascribed the carcinogenic action of these fatty agents to the oxysterol formed by heating.

Both the chemical and spectrographical determinations indicate, as already mentioned, a close relationship with other carcinogenic substances derived from the cholesterol, oxidated either by the action of ultraviolet rays or by heat.

I believe this research work to be a valuable contribution to the knowledge of the etiopathogeny of cancer, with reference specially to the value of the fatty substances, of animal as well as of vegetal origin.



Microphotograph 6—Higher magnification of the histological cut section of the same tumor, where the adenocarcinomatous process may be observed.



Scheme of the Lesions produced in the Stomachs in a series of 100 Rats

The carcinogenic process is ascribed to the sterols they contain and which are oxidized by heating.

The process observed has a long evolution — over a year — a fact that is in accordance with the observations made in the course of other experimentations of

the same kind, and which have been already reported. The development and evolution of these lesions correspond to a standard type which may be summarized as follows: 1st, epithelial hyperplasia; 2nd, ulceration, and 3rd, cancerization.

REFERENCES

1. A. H. Roffo—Formation of ulcers and malignant tumors in the digestive apparatus by ingestion of food with irradiated cholesterol. *Bol. Inst. Med. Exp.*, No. 46, page 589, 1937.
2. A. H. Roffo—Malignant tumors developed in the digestive apparatus by the ingestion of fat substances oxidized by heating. *Bol. Inst. Med. Exp.*, No. 48, page 539, 1938.
3. A. H. Roffo—See (1).
A. H. Roffo—Experimental gastric cancerization by ingestion of oxidized fats. *Bol. Inst. Med. Exp.*, No. 60, page 504, 1942.
A. H. Roffo—Fusocellular sarcoma of rat stomach; a consequence of fat feeding. *Bol. Inst. Med. Exp.*, No. 61, page 123, 1943.
A. H. Roffo—Carcinoma induced in a rat's stomach by ingestion of oil. *Bol. Inst. Med. Exp.*, No. 62, page 471, 1943.

EXPERIMENTAL SUMMARY

Rat number	Rat weight	Spleen weight	Relationship rat—spleen	Time of experiment days	Gastric Lesions
2	150	0.7	214	78	Malpighian zone, 5 ulcers; glandular, 4 ulcers
3	140	0.7	200	78	Malpighian zone, 11 ulcers; glandular, 6 ulcers
5	260	0.9	288	110	Glandular zone, 7 ulcers; abdominal tumor
10	140	0.9	155	167	Gland. zone, 13 ulcers
15	180	0.8	255	200	Malp. zone, 1 ulcer Gland. zone, 8 ulcers
16	210	0.7	309	209	Gland. zone, 7 ulcers; 1 large tumor
18	160	0.7	228	215	Gland. zone, 4 ulcers
19	170	0.7	242	220	Malp. zone, 4 ulcers; gland. zone, 9 ulcers and 1 great cancerized ulcer
20	230	1.5	186	232	Gland. zone, 11 ulcers; abdominal tumor
22	160	0.8	200	234	Gland. zone, 3 ulcers
26	180	0.9	200	247	Malp. zone, numerous ulcers with papillomatous edges; gland zone, 5 ulcers, 1 cancerized
27	210	1.0	210	247	Malp. zone, 1 ulcer; gland. zone, 13 ulcers; 1 abdominal tumor
31	210	0.8	262	255	Malp. zone, 8 ulcers; gland zone, 15 ulcers
34	145	0.6	241	263	Gland. zone, 7 ulcers
40	140	1.0	140	297	Malp. zone, 5 ulcers; gland. zone, 6 ulcers
42	125	0.7	178	327	Malp. zone, 3 ulcers; gland. zone, 1 ulcer and 1 large cancerized tumor
43	160	1.7	94	327	Gland. zone, 4 ulcers
44	200	0.9	222	336	Malp. zone, 10 ulcers; gland. zone, 5 ulcers

Rat number	Rat weight	Spleen weight	Relationship rat—spleen	Time of experiment days	Gastric Lesions
46	200	1.3	153	347	Gland. zone, 3 ulcers
47	220	1.2	183	350	Gland. zone, 8 ulcers
48	195	0.6	325	370	Gland. zone, 5 ulcers, abdominal tumor and tumor in the liver
58	160	0.4	400	422	Gland. zone, 3 tumors
61	240	0.8	306	460	Malp. zone, 1 ulcer Gland. zone, 9 ulcers
68	205	1.2	170	496	Gland. zone, 12 ulcers
72	180	0.9	200	502	Malp. zone, 3 ulcers; gland. zone, 8 ulcers
74	160	0.7	228	529	Gland. zone, 2 voluminous tumors and 6 ulcers
75	170	0.9	188	529	Malp. zone, papillomatosis; gland. zone, 7 ulcers
78	240	0.9	265	545	Malp. zone, numerous tumors; gland. zone, 8 tumors, 21 ulcers
83	210	0.8	262	570	Gland. zone, 5 ulcers
88	240	1	240	570	Gland. zone, 7 ulcers
89	220	0.8	275	570	Gland. zone, 2 ulcers, 1 tumor
91	230	0.7	328	570	Gland. zone, 5 ulcers
92	170	0.6	283	570	Gland. zone, 8 ulcers
93	210	1	210	570	Gland. zone, 1 tumor, 12 ulcers
96	215	1.9	113	570	Gland. zone, enormous tumor and 1 ulcer
97	195	1.6	190	570	Gland. zone, 2 tumors
98	305	1.7	135	570	Gland. zone, 3 ulcers
99	230	2	150	570	Gland. zone, 9 ulcers
100	300	1.2	162	570	Gland. zone, 1 tumor, 8 ulcers

Incidence of Appendicitis from a Survey of College Students

By
KARL A. STILES, Ph.D.*
and
FREDERICK W. MULSOW, M.D.
CEDAR RAPIDS, IOWA

THE incidence of appendicitis has been determined largely by estimates from mortality rates of appendicitis and hospital dismissals subjected to appendectomy. The present study was undertaken to learn more about the incidence of appendicitis among those who had reached college age.

Fowler and Boehrer (1) found an attack rate of 4 per thousand, per year among the student population of 15,000 at the University of Minnesota during the 10 year period studied. They say that this rate is less than half the national rate because many students reported to their family physician and in this way they could not be included in their student health data. A diagnosis of appendicitis was made in 594 students, and 310, or 52 percent, were not subjected to appendectomy. In 294 the appendix was removed. Of this number, 25 were considered as an interval type of operation, 222 had acute appendicitis, and in 37 the pathological examination did not reveal any evidence of an acute inflammation.

In the present study, 2968 students of Coe College were interrogated by questionnaires over an 8 year period. Of this number, 1175 were Army Preflight students. As a part of the entrance examinations they were asked to fill in the appropriate spaces by an "X" mark. They were informed of the nature of the study being made and were especially instructed to report facts only in the following blank given them.

QUESTIONNAIRE ON APPENDICITIS

Although a common affliction of modern man, little is actually known about the real causes of appendicitis. An investigation of this problem is being made among the students of this college, and your cooperation in giving the information asked for below will be greatly appreciated. Please mark an X in the appropriate spaces.

Age Sex: Male Female

Have you had your appendix removed? Yes No

If your appendix has not been removed, have you ever had an abdominal pain which a doctor has diagnosed as appendicitis? Yes No

Has any other member of your family had his appendix removed? Yes No If so, please state how related to you

If you come from a family in which there are several who have had their appendices removed, your name in the blank below will be appreciated.

Name

If you have had any other kind of an operation besides an appendectomy, please indicate in the blank below what it was.

The average age of the entire group was 19.47 years. It was recognized that few abdominal operations are performed for conditions other than appendicitis up to this age, but a question was submitted regarding other operations, and not more than 4 had other definite

abdominal operations. It can therefore be assumed that the large percent of those who had been subjected to an appendectomy, had a preoperative diagnosis of acute appendicitis. But a few may not have had an acute condition of the appendix at the operation. Other operations mentioned in reply to the questionnaire are shown in the following table.

Other Operations		Than Appendectomy Reported	
Tonsillectomy	1088	Pilonidal cyst	3
Mastoid	44	Knee cartilage	3
Hernia	42	Fistula	2
Nasal operations	21	Skull	2
Eye	9	Intestinal	2
Ear	6	Gall bladder	1
Lung and empyema	8	Hydrocele	1
Glands	6	Hypospadia	1
Hemorrhoids	5	Keloid	1
Tumors	5	Shoulder dislocated	1
Bone operations	5	Uterus operation	1
Leg and foot	10	Hip operation	1
Arm and hand	6	Other minors	22
Total	1255	Total	41
Total other operations			1296
Total appendectomies			297

Ten percent, or 297 of the 2968 students questioned, reported that their appendices had been removed. There were 199, or 9.6 percent of 2075 male students, who had been subjected to an appendectomy, and 98, or 10.9 percent of 893 female students. Among the men students there were 106, or 5.1 percent who had been told that they had appendicitis, but who did not have their appendices removed. Of the women students, 66, or 7.4 percent did not have their appendices removed for appendicitis.

Some surgeons believe that appendicitis tends to occur more in certain families, and attribute this to the family eating habits, or an inherited abnormal structure or location of the appendix. The evidence in this study is indefinite in regard to an inherited tendency.

DISCUSSION

The mortality of appendicitis had been increasing over a period of years. In the industrial policyholders of the Metropolitan Life Insurance Company, the deaths per 100,000 had increased from 15 in 1911 to 20.5 in 1935. But during the past 10 years the death rate has decreased at least 50 percent. This decrease is attributed to the use of sulfa drugs, improved surgical measures, and education of the public to the danger of the use of laxatives in appendicitis.

It has been stated by Osler (2) that 50 percent of the cases of acute appendicitis occur before the twentieth year. Among the college students we have found that about 10 percent have had their appendices removed. The average age of these students was 19.4 years. From these two figures it would appear that at

*Formerly of Michigan State College, East Lansing, Michigan.

least 20 percent of all people in the United States have an appendectomy during their lives.

Baker (3), from data obtained through the Literary Research Service of the American College of Surgeons, found that the death rate from appendicitis in recent years ranged from 13.7 to 17.4 per 100,000 population, and the mortality figures in hospitals was between 4 and 5 percent of appendectomies. From these figures he estimated that about 16 percent of the population would undergo hospitalization for appendicitis some time during their lives.

The mortality from appendicitis has decreased about 50 percent since this report by Baker. The Statistical Bulletin of the Metropolitan Life Insurance Company (4) says: "Although we have no conclusive data on the subject, reports of various investigators seem to indicate that the disease is not only more common today than it was a decade ago, but that its prevalence is still increasing." This may account for our figures on the incidence being higher than those obtained by Baker. Watkins (5) finds that appendicitis is increasing in frequency. He found that one person in 653 in Cleveland, Ohio, in 1941, had an acutely inflamed appendix removed, and in 1930 the figures were one in 832. Anderson (6) reports that about 750,000 people in the United States are hospitalized for appendicitis

annually. If this is true, about 0.5 percent of the population have an appendectomy each year. If this rate persists and our length of life is about 65 years, then about one third of all people would have their appendices removed during their lives.

This increasing incidence of appendicitis may be due to many factors. The education of the public as to the dangers of appendicitis, and improved diagnostic procedures are factors. If there is an inherited tendency in appendicitis, then early removal may prevent deaths of those having this inherited trait, but they consequently would be permitted to live and transmit this hereditary condition to their children, thus increasing the incidence.

CONCLUSIONS

In the present study it has been found that 10 percent of the 2968 college students questioned have had an appendectomy at some previous time. People of this age have few abdominal operations other than those for appendicitis. These students are largely from the middle class of the population. Perhaps 20 percent of the population in the United States have an appendectomy during life for appendicitis and an equal number do not have the appendectomy even though so diagnosed.

REFERENCES

1. Fowler, L. H., and Boehrer, J. J.: Appendicitis in College Students, Staff Meeting Bull. Hospitals of Univ. Minn., 11:344-361 (April 26) 1940.
2. Osler's Principles & Practice of Medicine, Christian, Appleton-Century Co., 1944, p. 700.
3. Baker, E. G. Stanley: A Family Pedigree for Appendicitis, The J. of Heredity, 28:187-191 (June) 1937.
4. Statis. Bull. Met. Life Ins. Co.: p. 6 (March) 1944.
5. Watkins, R. M.: Appendicitis in Cleveland, J. A. M. A. 120: 1026-1028 (Nov. 28) 1942.
6. Anderson, W. H.: A Compendium of Opinion, The Mississippi

Doctor, 20:366-369 (Jan.) 1943.

Contribution from the Science Laboratories of Coe College, No. 29, N. S., and St. Luke's Hospital. Aided by an Academy grant from the American Association for the Advancement of Science through the Iowa Academy of Science.

The Authors wish to acknowledge the assistance of Dr. W. N. Kreck and Dr. R. V. Drexler for their cooperation in collecting data for this study.

Endocrine Aspects of Obesity

By

MAX A. GOLDZIEHER, M.D.

NEW YORK, NEW YORK

IN the heyday of empirical medicine, it was almost axiomatic that obesity, unless due entirely to over-indulgence in food was, more often than not the result of an endocrine disturbance the characteristic signs of which permitted classification of obesity into gonadal, thyroid or pituitary types respectively. These views were based originally on the observation that castrated animals become obese. Spectacular gain in weight associated with some of the major endocrinopathies completed the evidence. Recent studies, however, do not bear out the view that obesity is consistently associated with manifest endocrine disorders. In a survey of 200 unselected cases of obesity (192 women and 8 men), Rony (106) found definite endocrine syndromes only in 13 patients; the diagnosis of "probable" endocrine disturbance" was made in 56 cases while 131 (65%)

were apparently free from glandular disturbance. The percentage of endocrinopathies was much higher in children or juveniles; a group of 22 boys and 28 girls—a total of 50 cases of obesity—showed 34 definite and 10 probable glandular disturbances while only 6 cases (12%) were "free". Thus endocrinopathies are far more commonly associated with obesity in children or adolescents than in adults. While the criteria used by Rony to exclude endocrinopathies are by no means convincing, clinical evidence definitely scales down the percentage of manifest endocrinopathies in obesity.

Anatomical studies of the endocrine organs of obese individuals are scarce and the available morphological descriptions are inadequate. Kup (67) reported 31 autopsies of an unselected obese material with "some pathology of one or several glands" in 26 cases. Lipomatosis and atrophy of the pancreas was most com-

mon. and varied changes of the pituitary, adrenals and ovaries were mentioned. Zeynek's (129) study of 32 cases also emphasized the lipomatosis and atrophy of the pancreas; 13 cases showed varied changes of the thyroid; 7 out of 17 cases examined showed adrenal cortical changes. The most important findings in respect to the pituitary were the conspicuous increase of basophilic cells. The highest cell counts were obtained in the most obese cases. The significance of basophilic hyperplasia in obesity was also described and emphasized by Kraus (65).

Our own anatomical studies frequently revealed minor lesions of the anterior pituitary such as interstitial fibrosis with or without focal round cell infiltration or degenerative changes including vacuolization and loss of chromophile granules (32). The findings, gathered in the course of the past thirty-five years, unfortunately cannot be expressed in statistical figures and hence are doomed to oblivion. The connection of pituitary tumors and obesity, on the other hand, is amply verified. Most chromophobe adenomas, even though strictly intrasellar, lead to obesity (21), in contrast to the eosinophile adenomas with symptoms of acromegaly which are usually not associated with obesity. The basophile adenoma, more often than not, is accompanied by overweight, irrespective of the presence of other symptoms of so-called basophilism.

Neoplastic conditions of the pituitary region such as suprasellar or anterior lobe tumors are common in Froehlich's syndrome, yet neoplasms have been found in the absence of obesity. In 149 cases of adiposo-genital dystrophy surveyed by Leschke (71), 21 were classified as mainly of pituitary origin; in 63 both the hypophysis and the floor of the third ventricle were involved, while in the remaining 65, "the hypophysis was intact or not seriously affected."

Thus, according to available records, the anatomical changes of the pituitary are inconsistent in obesity, hence the pathogenetic significance of this gland has met with doubt, especially since animal experiments are equally inconclusive. Total hypophysectomy without injury to the hypothalamus causes hypertrophy of the abdominal fat bodies in the tadpole (113). In the young rat, however, hypophysectomy does not cause adiposity but rather precipitates cachexia and precocious senility. Yet it must be emphasized that a totally hypophysectomized animal is a sick animal which does not feed well and this, obviously, interferes with growth or maintenance of body weight. In partially hypophysectomized animals, regenerative and hyperplastic changes of the remaining tissue are met with; the concomitant increased excretion of corticotrope hormone is followed by obesity (100). Kraus (65), who analyzed 12 cases of pituitary tumors associated with obesity came to similar conclusions, for the adrenal cortex was markedly enlarged and richly loaded with lipoids in all cases.

The significance of these cortical changes is substantiated by the obesity observed in cases of cortical tumors or hyperplasia. Successful removal of the tumor,

or resection of the hyperplastic adrenals is followed by spontaneous loss of weight (43, 123). These effects should be compared with the weight loss subsequent to adrenalectomy or Addison's disease and the gain in weight following administration of cortical extract. Increase in weight was also noted in experimental animals fed adrenal cortex or injected with cortical extract (78), and similar response was obtained in a variety of underweight patients (33, 45, 85).

The agreement is general that the fat depots in hyperinterrenal obesity are singularly resistant to dietary weight reduction. The lone dissenters from this view are Freyberg and Newburgh (28), who maintain that hyperinterrenal obesity is no different from other types and is readily controlled by dietary restrictions. This sweeping claim is based on a *single* case of Cushing's syndrome in which the weight was reduced at an accurately predicted rate. The patient, however, died in the course of weight reduction and the autopsy failed to disclose anatomical changes of the adrenals.

The adrenal cortex is not conceded a major role in the pathogenesis of obesity mainly because the fat distribution of hyperinterrenal cases is so distinctly different from ordinary obesity. The validity of this objection, however, deserves further, more critical evaluation.

Changes of other endocrine organs, including the thyroid and gonads, are neither consistent nor specific enough to warrant pathogenetic conclusions. The same can be said for the experimental evidence. Thyroidectomy is not followed, as a rule, by substantial gain in weight, nor is myxedema necessarily associated with obesity; the latter is more common in mild hypothyroidism, provided that the lessened caloric output is not compensated by decreased appetite and caloric intake. Nor does castration cause obesity in all animals; cattle and birds gain rapidly and extensively after castration, but the weight gain is definitely sex-linked, for it is far more conspicuous in the male. Castrated or menopausal women do not necessarily grow fat, although complete or partial insufficiency of the ovaries is likely to produce characteristic regional fat deposits, especially in the trochanteric area (25). It is the prevailing view that estrogenic therapy does not correct the general adiposity, nor does it help to reduce the trochanteric fat pads. In animal experiments, however, the weight gain of castrated rats could be corrected and even reversed to a loss by administration of estrone (109).

Investigation of the metabolism of obese patients has failed to furnish evidence of a uniform disturbance in the utilization of food or in heat production; hence, the complacent belief in the endocrine origin of obesity has lost its standing. The pendulum, as usual, swung in the opposite direction—so much so that obesity is no longer accepted as a metabolic disorder but rather as the consequence of excessive food consumption. The extreme protagonists of this view, such as Newburgh and his group (88), claim that the food intake always produces predictable changes in weight: gain follows overfeeding and loss follows subnutrition, ir-

respective of whether the food was consumed by normal, obese or lean individuals. Involvement of the endocrine system, if present, is coincidental or at best, "causes obesity through disturbance of appetite". These beliefs are supported by minutely performed metabolic studies which are so impressive at first glance that they have met with ready acceptance and only occasional timid objections. These conclusions, however, are based on purely circumstantial evidence and on assumptions, the validity of which has not yet been established. Thus, basal heat production is figured on the basis that caloric output is proportional to body surface and that the latter is adequately expressed by height and weight measurements. This calculation may be correct in normal cases but is highly questionable in the obese. Total heat production has been calculated on the basis that the water content of the fat tissue is constant at 10%, irrespective of changes due to a shift of water from its depots (92); and disregarding the contradictory findings of other investigators. Thus, Grafe (46) and his group found that the water content of the fat tissue varies widely: it may be as low as 5% or reach an extreme of 71% without any visible sign of edema.

An unprejudiced investigation of the problem of obesity should not start with the question why some people gain weight abnormally, but rather with the problem why all of us do not become obese, for most people regularly consume more food than required for maintenance (46). Obviously, anybody, who consumes food in excess of his individual requirements will gain weight, just as weight loss is inevitable on a starvation diet. These statements are as trite as they are misleading; for they fail to stress the individual nature of the caloric requirements and the wide range of their variability. Some of the factors responsible for this variability are well understood; they include physical activities and climatic conditions. The significance of endogenous factors in the determination of individual requirements, on the other hand, is not equally accepted by all and flatly denied by the "caloric" school, whose adherents maintain that the human body always produces heat in exact proportion to the amount of fuel intake, just as if it were a fuel burning engine. The fallacy of these views is readily demonstrable on chronically undernourished people who maintain their body weight or lose less weight and more slowly than the theory stipulates; similarly, some obese patients continue to gain weight in spite of a reduction of food intake well below the calculated requirements. Many obese people, moreover, reach a point where they do not gain more weight, although they do not change their eating habits; thus a balance appears to be established similar to that of the normal person between the ages of 25 and 40 who maintains a steady body weight without the need of curbing food intake. After the age of 40, a sudden increase of weight is often noticeable until it levels off again on a higher plane; all this happens without obvious changes in eating habits or physical activity. A personal observation may be pertinent: the writer's weight began to increase

a number of years ago and the gain could not be curbed until the food intake was reduced to less than 900 calories, 40% of which was protein. After an overall gain of 14 pounds, the weight became stationary and no more weight was added when the food intake again rose gradually to about 1800 calories by supplements of carbohydrate and fat. Environmental conditions and physical activities remained unchanged both during the periods of gain and stability.

Identical observations, made by many experienced physicians, serve as proof that the human body possesses means of adaptation which regulate body weight not merely by a change of appetite or physical activity but also by affecting body economy. If the regulatory mechanism breaks down, the gain in weight initiates the "dynamic phase" of obesity; the "static phase" is attained when the process comes to a halt, as a sign that a new balance has been established which is again competent to regulate the utilization of ingested food.

The conflict between theory and actual clinical observations is due to several misconceptions, the most important of which concerns the meaning of "*basal oxygen consumption*." This phrase is supposed to express the sum total of all metabolic processes which must be maintained by the ingestion of food, for a caloric deficit would compel the body to burn up some of its own substance, chiefly the depot fat. Included in these metabolic processes are: 1. the actual heat production and, 2. the energy required for the maintenance of respiration, circulation and other smooth-muscle activities. *The energy requirements for the chemical processes performed by the cellular protoplasm throughout the body are usually left out of calculation.* As studies with heavy hydrogen or other "tagged" atoms have shown, the cytoplasm is subject to much more active changes than previously believed, for there is a constant catabolism or breakdown of protoplasmic constituents followed by immediate replacement. These continuous changes in the proteinous elements of the cytoplasm are accompanied by new formation of glycogen from amino acids or fatty acids, often followed by conversion of glycogen into fat for the purpose of storage. Nor is the ingested fat deposited in the subcutaneous tissue necessarily in its original form; at least some of the fat molecules are broken down and rebuilt before being stored. All these chemical processes require energy which is supplied by oxidation, yet this part of oxygen consumption does not figure in the heat production in the ordinary sense of the word. Oxygen consumption in the fasting and resting state actually expresses not merely the basic requirements for heat production and autonomic activity, but also includes other, oxygen-consuming *cellular activities* of undetermined magnitude. It is hardly probable that these cell functions are basic, in the sense that they proceed at the same rate at all times; it is more likely that they decelerate, at times, if so demanded by adaptation to circumstances; or they may go on at a rate much higher if speeded up by metabolic or hormonal stimulation. There are no methods known to determine the exact oxygen consumption which these

cellular activities require; yet their very existence offers a plausible explanation for otherwise paradoxical facts such as the persistent weight gain in spite of reduced caloric intake in the dynamic phase of obesity or the equally puzzling phenomenon of static obesity, i. e., unchanged body weight without decreased food intake.

Methods previously used to investigate the "intermediary metabolism" include determination of the nitrogen balance and of the respiratory quotient. Both procedures, however, show only the overall end results of a complex chain of events and do not clarify the intermediary steps. Thus nitrogen equilibrium, i. e., nitrogen elimination equalling nitrogen intake, does not preclude a massive breakdown of body proteins, provided that the metabolites are resynthesized to form new protein. Similar objections have been raised against the prevalent interpretation of the respiratory quotient as evidence of the relative amount of carbohydrate, fat or protein metabolized (115). Cognizant of these objections, we may still quote the claim that the obese, after being fed a protein or fat meal, show an R. Q. indicative chiefly of carbohydrate and but little fat utilization, whereas in thin or normal subjects, the energy is derived from the utilization of the ingested protein and fat (117). Other studies of the R. Q. seemed to indicate that a synthesis of fat from glucose characterizes obese persons (4, 48). It is in line with these views that the R. Q. was found to be substantially increased in obesity due to experimental injury to the hypothalamus; the rise of the R. Q. during the period of rapid weight gain was far in excess of that observed in the control animals fed an identical diet. Once the animals had reached the static phase of obesity, the R. Q. remained on a lower plane (15). These observations were interpreted as suggesting that the conversion of food to fat proceeds at a much higher rate following hypothalamic injury.

The processes which increase or lessen energy expenditure and thereby succeed in maintaining body weight and subcutaneous fat deposits are part of the mechanism which stabilizes the internal environment. This mechanism disposes of excess calories or "balances the budget" on a lower intake level in the normal person, except in overfeeding or in starvation, sufficient to break down the equilibrium of the best balanced organism. Such a breakdown, however, occurs more readily in constitutionally predisposed individuals whose inclination to become lean or obese appears to carry the stigmata of heredity.

The second misconception relates to the view that obesity is an entity and not a mere symptom of varied origin. Recognition of the dynamic and static phases of obesity already established the complexity of the problem. Even more significant are the differences between the fat stored more or less evenly all over the body and that which accumulates only in certain regions: the former is truly dependent upon the caloric equilibrium (food intake and energy output), whereas the regional fat deposits remain largely outside the general economy, for they do not seem to participate

in the general weight loss caused by subnutrition. This relative independence of the general state of nutrition is demonstrable experimentally: the regional distribution of fat in rats varies according to sex and age, but not according to the type of diet, irrespective of whether a high carbohydrate or a high fat diet is fed or whether almost half of the body weight is removed by subnutrition (97). Even more striking were observations in humans in which abdominal skin was used for grafting to cover skin defects on the hands or face. Many years later the patient developed abdominal obesity and simultaneously, the subcutaneous fat accumulated in the transplanted skin, strikingly demonstrating that the tendency to deposit fat was inherent in the abdominal skin (56, 116). Thus a new factor enters the problem—the fat tissue itself, and its activities in the accumulation and retention of fat. The forces which govern the "lipopexic" function of the fat tissue are not yet understood although influences exercised by the nervous system are demonstrable. Sectioning of the nerves which lead to the fat tissue causes characteristic changes of the fat cells and alters their reaction to underfeeding or overfeeding (5, 11, 50, 68).

The assumption that obesity is an *entity* is particularly misleading in the interpretation of metabolic studies on the obese. Most of the statistically presented data are supposed to show that the metabolic rate, the specific dynamic action of proteins, the blood sugar, the sugar tolerance or fat metabolism in the obese, do not deviate consistently from those in non-obese controls. Most significant is the claim that carbohydrate metabolism is normal in the obese and that "no one has demonstrated low blood sugar in patients whose main complaint is obesity" (88). These statements are at variance with our own data and are contradicted also by other investigators, for instance Rony (106), who found in a series of 166 unselected cases of obesity, 9 cases of fasting hypoglycemia and 16 of hyperglycemia. The sugar tolerance test performed on this group produced a normal curve in only 60% while tolerance was increased in 19 and decreased in 21%. In a separate group of 46 juveniles, sugar tolerance was high in 36% and low in 18%, a total of 54% abnormalities.

The conclusion that obesity develops independently of all metabolic abnormalities, arrived at without consideration of contradictory evidence, cannot be accepted as valid because it is based on data obtained on a mixed population with only one symptom, that of obesity, in common. In patients whose obesity is due to overfeeding, deviations from the normal averages are not expected whereas significant variations are obtained in the presence of endocrinopathies. Statistical studies on an unselected group, including both simple and endocrine obesity, cannot produce significant data.

If, however, obese patients are divided in suitable subgroups, a definite metabolic pattern emerges which, particularly in pituitary obesity (37, 44), appears to be characteristic of the endocrinopathy itself rather than

the obesity, yet seems to contribute, directly or indirectly, to the accumulation and maintenance of fat deposits.

In order to appreciate the participation of the endocrine glands in the pathogenesis of obesity, it is necessary to survey the individual factors which contribute to the deposit of fat and to investigate the relationship of the endocrine system to each of these factors. Our survey will outline the pertinent facts according to the following tabulation:

A. Excessive food intake due to:

1. increased appetite
2. delayed satiation

B. Decreased caloric expenditure due to:

1. inactivity
2. decreased basal metabolism
3. decreased Specific Dynamic Action of Proteins
4. decreased "luxury consumption"
5. decreased heat loss and greater economy in muscular work
6. abnormal intermediary metabolism

C. Disturbances of the fat tissue:

1. lipophilia
2. decreased fat mobilization
3. abnormal fat metabolism

D. Water retention

E. Heredity and constitution

F. Precipitating Factors:

1. critical periods (puberty, pregnancy, menopause)
2. convalescence (post-infectious, post-surgical)
3. tonsillectomy

A. EXCESSIVE FOOD INTAKE

Excessive food intake is explained as the result of environmental conditions, habit, enjoyment of eating or psychogenic influences. The psychological interpretation of overeating as the principal cause of obesity has gained increasing popularity in recent years. "Anhedonic obesity", an expression coined by Myerson (87), points to the crux of the problem: the substitution of the pleasure obtained by eating for other gratifications of the ego which are denied by the circumstances. The significance of emotional factors in the overfeeding of children was correctly emphasized by Bruch (16, 17), who cautiously stated, however, that "inordinate intake of food is only one factor among many" and that her studies on childhood obesity lead to "conclusions which do not imply that the endocrine balance of obese children is normal." Far greater and practically exclusive emphasis was laid to the motivation and symbolic meaning of overeating by Richardson (103), in whose opinion obesity is the direct product of neurosis, for he states that "successful reduction of weight depends on the degree to which the psychological factors are understood by the patient or utilized in the treatment by the doctor."

The importance of psychological factors should not

be denied, yet logic demands that if an obese patient happens to be neurotic, the neurosis does not necessarily precede or cause the obesity. Experience obtained on more than 3000 cases of obesity on clinic patients as well as in private practice has convinced us that weight reduction often ameliorates the neurosis of the obese and may even eradicate all its manifestations. These observations justify the conclusion that neurosis in the obese may be conditioned by the patient's unfavorable appearance and inadequate performance with attendant feelings of inferiority. As soon as normal body contours are regained, the patient's outlook on life changes in the direction of a normal attitude towards his own person and its relationship to the outside world. The obese patients who attended the clinic in numbers far too large to permit individual psychological attention, received only routine treatment, yet still made excellent progress, contrary to Richardson's postulates.

Increased appetite or craving of certain types of food is not governed merely by the seeking of pleasure by habit or environmental influences, but to a considerable degree by nervous centers, the autonomic nervous system and the endocrine glands. The inadequacy of explaining increased food intake on the basis of environmental conditions is documented by the observation that "obese as well as thin children are frequently found in the same family although they are offered the same kind and amount of food by the same parents" (106). It should be borne in mind, moreover, that increased appetite and food intake is, at least in part, the result rather than the cause of obesity. Thus heat production in the fat, yellow mouse is 6.44 calories in contrast to the 2.85 calories in the normal white animal. Calculated per Gm. body nitrogen, the rate is 10.5 against 5.56 calories, i. e., there is practically double the energy produced in the fat animal (8). The large body surface of the obese requires a high maintenance energy which is expressed either by a higher basal metabolic rate or, more accurately, by an increased 24 hour resting heat production (106), which automatically calls for greater caloric intake.

The influence of higher nervous centers upon appetite is demonstrable in animals by experimental lesions in the hypothalamus following which food intake increases and obesity develops rapidly (52). The mechanism of the hypothalamic influence upon both appetite and obesity is not yet fully understood, but it is claimed to be independent of the pituitary, because it has been noted that in many cases of brain injury associated with obesity, the pituitary reveals no manifest changes. The hypophysis was alleged to be intact or "not seriously affected" even in 65 of 149 cases of typical adiposogenital dystrophy gleaned from the literature (71). Moreover, hypothalamic obesity can be produced in the hypophysectomized animal; nor is the progress of hypothalamic obesity interrupted by subsequent hypophysectomy (55). On the other hand, obesity is greater if the anterior lobe of the pituitary is left intact apparently because its trophic hormones are needed to maintain the function of the adrenal cortex as well as that of the gonad and thyroid, all of

which are not negligible factors in the development of experimental hypothalamic obesity (51). The significance of the posterior lobe is much more definitely known, for destruction of the neurohypophysis elicits retrograde degeneration of the paraventricular nuclei (29, 51), and produces the same type of obesity as does direct injury to the hypothalamus.

1. REGULATION OF APPETITE

There can be no doubt that the endocrine glands contribute to the regulation of appetite. A complete loss of appetite is conspicuous in the hypophysectomized or adrenalectomized animal as well as in comparable human conditions such as Simmonds' or Addison's disease. Administration of pituitary extract restores the appetite in the hypophysectomized animal and increases it in normal, young animals (95). Injection or oral ingestion of cortical extract is similarly effective both in humans and experimental animals. Marked anorexia develops after parathyroidectomy especially against phosphorus-rich food (112). Hytakerol or vitamin D increase the voluntary phosphorus intake as well as the appetite of the parathyroidectomized rat and reduces calcium hunger (105). The adrenalectomized rat also manifests increased appetite for sodium chloride and decreased appetite for carbohydrate with a striking reversal upon administration of cortical extract or desoxycorticosterone (104).

The blood sugar is one of the most important metabolic factors in the regulation of appetite. Hypoglycemia produced by the injection of insulin causes hunger and demonstrable contractions of the gastrointestinal tract (18). The hunger contractions are promptly relieved by the administration of either glucose or atropine. Craving for food and especially for sugar is a common but not invariable symptom of spontaneous hypoglycemia; carbohydrate hunger was demonstrable only in 34 out of 112 cases of hypoglycemia (36). Increased hunger is also common in hyperglycemia, especially in the diabetic, hence it is not the actual level of the blood sugar which elicits the manifestation of hunger. It is rather the lessened availability of glucose for utilization in the tissues and especially in the musculature which causes reactions. Utilization of sugar is reduced in both diabetes and hypoglycemia, hence the increased appetite and craving of carbohydrates in both conditions.

The appetite is often strikingly increased in Graves' disease; the increased food intake may prevent the loss of weight in spite of the greatly increased metabolism. Rapid loss of weight ensues, however, as soon as the appetite is interfered with. The specific effect of the thyroid hormone upon appetite is corroborated by observations on myxedematous patients whose appetite is usually reduced; consequently their weight does not increase materially or even decreases in spite of the greatly reduced metabolism.

It is fair to conclude, therefore, that the endocrine glands influence appetite either directly or indirectly by interference with normal carbohydrate and electro-

lyte metabolism or with heat production in general. The influence of the endocrine glands is mediated partly by the autonomic nervous system which largely controls contractility and secretory functions of the gastrointestinal tract.

2. SATIATION

The feeling of satiation is important in the regulation of food intake. Hungry — and more particularly, starved individuals may feel satiated after eating a small meal; in others, satiation may not become manifest even upon eating a great deal more. Booth and Strang claim that the rise of skin temperature up to a maximum of 2° C. within one hour after eating, is instrumental in preventing further food intake. This regulatory reaction is particularly marked upon ingestion of proteins, for it is based upon the *specific dynamic action*. The endocrine implications of the latter will be discussed subsequently.

B. DECREASED CALORIC EXPENDITURE

1. INACTIVITY

Caloric expenditure can be lessened and part of the ingested food thus saved for conversion into fat by several factors, among which physical inactivity is the most obvious. Inactivity may be due to environmental influences, physical incapacitation, or emotional disturbances, yet the influence of endocrine factors is also apparent. Thus, sluggishness is a common symptom of hypothyroidism even though thyroid deficiency has not reached the degree of myxedema. With decreased desire for activity and with performance on a lower plane, less energy is consumed. Lethargy, even greater than in hypothyroidism, is noted in some of the organic or functional disorders of the pituitary and similar lethargy or actual somnolence is an outstanding symptom of severe hypoglycemia. The influence of the gonads on physical activity needs no further comment. Its practical application is demonstrated in animal husbandry, for the castrated animals are not only less active but gain weight as well. This response is more marked in the male, than in the female animals, which is in accord with the clinical observation that a decrease or loss of sexual urge and androgen production in the middle aged male usually coincides with decreased physical activity and increased fat deposits.

Asthenia is an outstanding symptom of Addison's disease and is equally characteristic of the adrenalectomized animal. Administration of cortical extract restores normal vigor and physical activity. Cortical therapy is strikingly effective in the asthenia of patients who are convalescing from infectious diseases (33). Muscular fatigue is also a common symptom of diabetes mellitus; it contributes to the sedentary habits and the gain in weight while appropriate insulin therapy is apt to restore an adequate degree of physical endurance.

2. BASAL METABOLISM

It seems to be the consensus of opinion that the basal

metabolism is not substantially decreased in obesity; as a matter of fact, if calculation is based on the ideal body weight, the basal metabolism of the obese appears to be actually increased (89). The available data, however, are of relative value only because they refer to unselected cases of obesity thrown together in one group, irrespective of their divergent pathogenesis. Separation of the endocrinopathies from the merely overfed, reveals a tendency toward a lower metabolic rate (44). This applies not only to clear-cut cases of hypothyroidism which form only a small percentage of the obese population, but particularly to the much larger pituitary group. No consistent changes are noted in obese patients with hypogonad or hyperinterrenal background.

3. SPECIFIC DYNAMIC ACTION

The role of the S. D. A. of proteins is similarly obscured by the prevalent mistake of studying the problem on an unselected material. This explains the controversy between those who claim that the S. D. A. is decreased in obesity and those who found no essential difference between the S. D. A. of obese, normal or thin individuals. It is quite apparent that neither overfeeding nor the subsequent obesity will change the S. D. A. of proteins. Ample evidence, on the other hand, points to a significant decrease of the S. D. A. in pituitary deficiency, irrespective of whether the hypopituitary patient is obese or emaciated (39). Most of the earlier work concerning the relationship of the S. D. A. to pituitary disease by Plaut (94), Liebesny (74), and others was rejected on the basis of two later contributions (61, 30). Johnston studied 6 cases of pituitary disease and found adequate heat production after ingestion of 300 Gm. of steak. The use of a large protein test meal, however, makes these findings misleading, for differences in the S. D. A. become apparent only if much smaller protein test meals are used, as for instance the white of three eggs (39). Fulton and Cushing studied the S. D. A. on 21 cases of acromegaly, 32 cases of hypopituitarism due to pituitary tumors, 16 cases of parhypophyseal tumors and 13 controls. The material, unfortunately, is quite one-sided: it consists exclusively of tumors which may affect pituitary function in divergent ways. A critical review of this paper (35) has pointed out that the S. D. A. is either normal or increased in the majority of chromophile tumors capable of carrying on the secretory function of the glandular tissue. Hypopituitarism occurs only in the non-secretory tumors, provided that the growth destroys or produces atrophy of the anterior lobe. Studies performed first on a group of 264 patients (39) and subsequently, on an even larger material including several hundred controls (35, 44) have shown that with the technique of a small protein meal, the S. D. A. is significantly decreased or absent in cases of clinical hypopituitarism while a definitely increased S. D. A. occurs in secretory pituitary tumors as well as in eunuchoidism or in menopause in which functional hyperpituitarism is demonstrated by the increased excretion of gonadotropins

in the urine. The increase of the S. D. A. to a normal level following prolonged organotherapy of hypopituitary patients is additional corroborating evidence of the views presented (39).

The results of animal experiments are less clear-cut. Houssay (59) performed hypophysectomies with or without thyroidectomy and concluded that the pituitary does not influence the S. D. A. in the dog, although he concedes that this must not be the case in other species. Analysis of Houssay's data reveals that the heat production increased in the hypophysectomized dog following the intake of 300 Gm. of meat, yet the rise was 35% less than in the non-operated controls. That hypophysectomy in dogs does not abolish the S. D. A., particularly upon ingestion of large amounts of meat, seems to be corroborated by others (6). In other animals such as the rat, however, ingestion of the amino acid glycine failed to produce the increase of metabolism which it does in normal animals; when the hypophysectomized animals were treated with pituitary extract, normal dynamic effects were obtained (27).

In view of the admitted importance of species differences, the fact that hypophysectomy in the dog does not completely abolish the S. D. A. does not justify the unwillingness to credit consistent clinical findings which were obtained on several hundred patients. This reticence is even less justified in view of the well-established influence of the anterior lobe on metabolism. This influence is exerted indirectly through the thyrotropic principle by mediation of the thyroid and directly by other pituitary factors, such as prolactin or the *specific metabolic principle* of Collip, which are both capable of increasing oxygen consumption in the thyroidectomized animal (92, 102).

The mechanism by means of which the pituitary affects the S. D. A. of proteins is not yet clearly understood. Most of the excess heat production probably occurs in the liver where metabolic activities are stimulated by the anterior lobe. Hence, the decreased or absent S. D. A. of the hypopituitary patient expresses a functional disturbance of the liver—a concept well in accord with Rowe's (108) findings that liver function is frequently impaired in pituitary disease. Further corroboration is offered by the practically consistent increase of the blood uric acid in hypopituitary patients (44, 108, 122).

4. "LUXURY CONSUMPTION"

Luxury consumption is a term used by Grafe (46) to describe the ability of the body to dispose of excessive calories by an increased rate of oxidation. Grafe believes that the S. D. A. of food cumulatively increases in the course of chronic overfeeding. Failure to respond with this cumulative increase yields deposits of fat and constitutes one of the major causes of obesity. Unfortunately, Grafe limited the meaning of the term, "luxury consumption" to the ability of the body to dispose of excess calories with the help of the S. D. A. and did not emphasize the possibility of other ways of consuming energy which, if restricted,

would lead to the conversion of food into depot fat.

Newburgh (89) completely rejects Grafe's luxury consumption, mainly because careful study of a single case of extreme subnutrition did not confirm the overstimulation of metabolic activities by super-alimentation.

As this controversy is essentially related to the question of the S. D. A., it is clear that all endocrine factors capable of influencing the former, are of equal importance in producing the cumulative effects of luxury consumption. Hence, insufficiency of the anterior lobe must materially decrease the ability of the body to dispose of excess calories as the normal person does successfully to prevent the deposition of fat.

5. HEAT LOSS AND WORK ECONOMY

Grafe does not claim that luxury consumption is the sole safety valve which prevents the accumulation of fat and emphasizes the greater economy in the expenditure of energy in the obese. This was demonstrated by experiments on obese people trained to lift weight who accomplished their task with less caloric expenditure than required by control subjects of the same height and age. The saving of energy amounted to about 28% (31). Long term studies also show additional economies of energy by the obese: their metabolism after physical work may increase to the expected level in the beginning; subsequently, however, the metabolic activities slow down considerably over a prolonged period of time so that the total heat production over the combined period is definitely less than in the controls (9). Contradictory findings, calculated indirectly on the basis of still unproven assumptions, were obtained by Newburgh et al. (90). Bernhardt's (9) findings, on the other hand, are in accord with the observation that heat loss from the uncovered body surface is lower in the obese than in normal controls, thus permitting additional saving of energy (81).

Whether or not the endocrine glands play a role in the regulation of energy requirements by curbing unessential expenditure such as heat loss from the body surface, has never been investigated. The regulation of body temperature and heat loss from the body surface is primarily under the influence of the midbrain and the autonomic nervous system, but in view of the intimate interrelation of the latter with the endocrine system, hormonal influences are certainly not negligible. Similarly, the expenditure of energy by muscle work depends upon complex metabolic processes in the contracting muscle tissue, which are closely linked to the metabolism of carbohydrates. Physiologic maintenance of the latter depends upon the well balanced function of pancreatic islands, anterior pituitary and both components of the adrenal glands. This is borne out by common clinical knowledge; thus, muscular weakness is an outstanding symptom of diabetes mellitus and Addison's disease; it is apparently related to abnormalities in the utilization of carbohydrate by the muscle which can be corrected with relief of symptoms by administration of insulin or cortical extract

respectively. Muscular strength and working capacity is greatly influenced by androgenic sterols while the effect of the thyroid hormone is also undeniable although its mechanism is still obscure.

6. INTERMEDIARY METABOLISM

Cellular anabolism, i. e., the rebuilding of protoplasm for the replacement of losses sustained through continued catabolic processes, occasions considerable consumption of energy. The expenditures involved in these complex phenomena, unfortunately, have not yet been measured. Hormonal influences which regulate these processes, however, are clearly demonstrable. Thus, cytoplasmic protein is readily formed under the influence of androgenic sterols as demonstrated by retention of nitrogen, sulphur, potassium and phosphorus, following the administration of testosterone (98). Some of the new tissue protein is produced at the expense of circulating plasma proteins (1, 127), but this does not necessarily decrease the energy requirements for the synthesis of specific cell protein. Nor is the influence of the thyroid hormone on cellular metabolism merely one of increasing the oxidation of ingested calories. Lack of thyroid hormone accounts for stunted growth, often readily relieved by thyroid medication; the increased rate of growth plainly indicates that the thyroid hormone is needed for building new body substance. Another convincing proof of the anabolic activity of the thyroid hormone is its effect upon the differentiation of tissues as shown first on tadpoles (47).

The growth promoting activities of the anterior pituitary permit the same interpretation. The anterior lobe hormones increase not only the growth of the bones, but also the size of the viscera which, on the other hand, decrease after hypophysectomy and increase again upon adequate pituitary substitution therapy. Another significant example of the anabolic phenomena elicited by hormones is the case of the lactating mammary gland; the secretion of the breast gland is predicated on the combined effects of the two ovarian hormones but eventually depends upon the secretion of prolactin by the anterior lobe.

More evidence is offered by studies on the endocrine glands in case of subnutrition or overfeeding. Prolonged subnutrition of the rat produces adrenal atrophy comparable to that obtained by hypophysectomy, yet these changes are readily repaired by pituitary substitution therapy (86). Thus the secretion of the anterior lobe shuts down in subnutrition and its hormones, as well as those of the adrenals, thyroid and gonads fail to carry on the physiologic stimulation of cellular anabolism. Overfeeding, especially of fat and protein, causes considerable increase in the size of the adrenal cortex associated with increased secretory activity; the latter is demonstrated by the maintenance of liver-glycogen stores in such animals even after a 24 hour fast (83). This completes the cycle: a food deficit decreases hormone output and depresses cellular life to a plane of lessened activity and expenditure, whereas overfeeding increases hormone secretion as a help

to the tissues of the body to carry on a more active or even wasteful level of cellular metabolism.

A further example of hormone influence upon synthetic activities of cells is offered by the function of the thyroid, adrenals and gonads, for the maintenance of their structure and secretion depends upon stimulation by the trophic hormones of the anterior pituitary. Elaboration of thyroxin or of the sterols of the sex glands and adrenals is undoubtedly an energy-consuming process which must be preceded by assimilation of building material and further synthesis in the cytoplasm of the secretory cells in order to form the complex hormone molecules. Similar anabolic processes take place in the pituitary gland under the stimulation of various hormones which, if given in suitable dosage, increase the output of gonadotropins, thyrotrophin or adrenotropin.

C. DISTURBANCES IN THE FUNCTION OF THE FAT TISSUES

1. LIPOPHILIA

The "caloric" school is inclined to disregard the active participation of the fat tissue in the maintenance or increase of body weight and looks upon it as if it were a simple connective tissue loaded with fat and acting as a passive receptacle. Wells (124) has taken issue with these views by pointing out that not every fibroblast is capable of forming adipose tissue since there is fibrous tissue which never produces fat cells. The specific nature of the adipose tissue is strikingly demonstrated by the formation of "glandular" fat organs. These lobular bodies are formed from capillaries and reticulum cells in a manner comparable to the formation of lymphoid tissue; the close relationship with the latter is further attested by the tendency of fat tissue to replace lymphoid tissue. Wells concludes that the adipose tissue is part of the reticulo-endothelial system and as such partakes in its varied functions, even though the fat cells are quite distended with fat. To prove this contention experimentally, Wells poisoned dogs with phosphorus or phenylhydrazine and obtained massive fatty changes of the liver, yet these livers oxidized uric acid just as well as the non-fatty liver of the control animals.

The functional activity of adipose tissue is attested by the great variability of the fat stored: only 60% consist of neutral fat while the rest is made up of phospholipids, cholesterol esters and other unidentified lipids in widely varying proportion (106).

One of the important functions of fat tissue is to take up glucose from the blood and convert it into glycogen. Up to 7% glycogen has been found in the fat tissue a few hours after a rich carbohydrate meal, especially following prolonged fasting (126). The fat cells take up glucose from the hyperglycemic blood and either store it as glycogen or transform it into fat (3). Some of the glycogen is reconverted to glucose and released into the circulation or metabolized into lactic acid as shown by *in vitro* experiments (57). Lactic acid is also formed *in vitro* by glycogen-free fat tissue if glucose, galactose or fructose is added to

the medium. Insulin promotes these metabolic activities, especially the formation of glycogen (75, 111). The glycogenopexic function of fat tissue apparently plays a role in the maintenance of normal blood sugar levels, for it drains the postprandial excess of sugar from the blood at a time when its oxidation with the help of insulin is not yet in full swing. It seems that adipose tissue overloaded with fat is not capable of adequately removing glucose from the blood; this failure would explain the hyperglycemia commonly noted in non-diabetic obese subjects which is readily corrected by weight reduction.

The special lobular fat bodies store more glycogen than ordinary fat tissue; they also use more oxygen *in vitro* while their R. Q. never rises above 1 (24). Large amounts of lobulated glandular fat tissue are deposited in some animals, as for instance in the tail of the "broadtailed" sheep. Amputation of this tail elicits a considerable rise of the R. Q. as a proof of the metabolic activities of this tissue (124). The glandular fat, on the other hand, is far more resistant to depletion than ordinary fat tissue; its refractoriness to participate in energy production for the rest of the body practically equals that of a lipoma.

The human body also contains glandular fat tissue characterized by similar resistance; thus the sucking fat pads in the cheeks of infants remain practically unaltered even in advanced emaciation. Glandular fat tissue is particularly conspicuous in the cretin and, though resistant to starvation, readily shrinks upon administration of thyroid (124).

The reticulo-endothelial cells, according to experimental evidence (40), are selectively influenced by hormones which either stimulate or inhibit their function as gauged by the storage of particles, cholesterol or bile pigment. The specific effects of hormones upon these cells justify the view that the reticulo-endothelial system becomes a functional entity only by virtue of the controlling influence of the endocrine glands (34). It is logical, therefore, to assume that the adipose tissue, in view of its reticulo-endothelial origin, is controlled by the same forces. Clinical and experimental data support the view that fat storage is subject to hormonal influences. Thus injection of insulin in the experimental animal as well as in humans promotes the deposit of fat; similar effects are obtained by feeding or injecting cortical extract (33, 119). The characteristic weight loss of the adrenalectomized animal cannot be corrected even by forced feeding of fat (99, 101).

Several investigators have claimed that obesity is due to a lipophilia of the fat tissue, the increased avidity of which in circumscribed regions would explain the origin of localized fat deposits. The selective regional distribution of fat is quite common. In a study of 200 unselected obese patients, Rony (106) found marked localized deposits in 41 cases. The character of the distribution is, at least partly, determined genetically; other deposits obviously develop under the influence of the sex glands; predilection to the upper body is characteristic of the male and lower body de-

posits of the female type. Accentuation of the male or female body contours at the time of pubescence emphasizes the influence of the sex glands. Similarly, the lack of sex hormones in the castrate accounts for specific regional fat deposits.

Long ago, clinical experience associated selective accumulation of fat with various endocrinopathies such as hypothyroidism, pituitary insufficiency or adrenal cortical hyperactivity. These associations are borne out not only by the varied symptoms indicative of the particular endocrinopathy but primarily by therapeutic observations: e. g., removal of a hyperactive cortical tumor is followed by a return of normal body contours. Similarly, thyroid or pituitary substitution therapy is likely to cause a far better redistribution of fat than that accomplished by mere dietary weight reduction. The significance of endocrine factors in the abnormal distribution of fat is admitted even by those (20a) who deny all endocrine influences in the pathogenesis of obesity—a rather illogical attitude, for factors capable of producing, e. g., a buffalo neck or full moon face, should not be incompetent to promote fat accumulation throughout the body.

The regional accumulation of fat is, in the opinion of Wells (124), intimately related to an abnormal function of the endocrine glands and particularly, to genital hypoplasia. Wells states emphatically that lobular fat is far more widespread in endocrine adiposity, especially, of the hypophyseal type or in castrates; other regional deposits in the obese, however, display the histology of ordinary fat tissue.

The classical example of regional lipophilia is the syndrome known as progressive lipodystrophy. The abnormal fat deposits are usually limited to the lower half of the body whereas the face, neck, and trunk may show considerable emaciation. Simultaneously, there is a definite increase in the basal metabolism. Administration of thyroid increases the emaciation of the upper part of the body whereas the obese, lower half remains untouched by the medication or may even accumulate more fat. This shows clearly that fat tissue, though not neoplastic, may still ignore such general metabolic stimuli as the thyroid hormone which is effective upon other tissues while the abnormal fat remains outside the general body economy. Refractoriness to thyroid medication is also occasionally observed in other cases of obesity; it may develop in persons who previously responded normally to average doses by a loss of weight and increase in basal metabolism. One of these refractory patients consented, for experimental purposes, to take up to 20 grains of U. S. P. thyroid daily without sustaining a loss of weight or an increase in pulse rate and basal metabolism. Similarly resistant are the trochanteric fat pads or "breeches" in hypogonad or menopausal women; they remain largely unaffected even after considerable weight reduction by dietary means.

2. FAT MOBILIZATION

Participation of the fat tissue in the general economy of the body depends upon the availability of the

depot fat. Abnormal, i. e., too slow mobilization of fat in the obese was claimed on the basis that the total fatty acid content of the blood plasma dropped about 40% in obese patients who were kept on a low caloric diet for a period of 8 days whereas no comparable changes occurred in normal controls (54). Abnormal blood fat curves following the intake of a fat meal were also observed (66). The alimentary lipemia is either decreased or increased in obese patients; these changes in fat tolerance, however, seem to parallel the sugar tolerance (106).

Injection of pituitrin is supposed to decrease or abolish the alimentary lipemia in non-obese subjects whereas no such effects are obtained in the obese (96). Pituitrin also inhibits the hypercholesteremia which develops in obese patients following the ingestion of cream (13).

Hypophysectomized rats lose 28% of their body fat and 19% of body protein whereas identically fed controls lose no protein but 60% of their body fat. This would indicate that the pituitary contributes to the mechanism which mobilizes fat from the depots in order to supply energy (69)—a view supported by the observation that repeated injections of anterior lobe extracts produce fatty livers, accompanied by ketonuria and a decrease of body fat in fasted rats (10).

Fat mobilization is influenced also by the adrenal cortex, for phosphorus poisoning in the adrenalectomized rat fails to produce fatty liver, whereas fatty changes develop upon injection of cortical extract (76, 121).

Hyperlipemia, i. e., excessive mobilization of fat in diabetes or nephrosis rapidly decreases upon administration of insulin, hence it could be argued that hyperlipemia, at least in diabetes, depends to a certain extent upon the inadequacy of insulin supply.

3. FAT METABOLISM

Abnormalities of fat metabolism have been noted in obesity: the increase in ketone bodies which ordinarily follows hyperventilation or the intake of alkalis is supposed to be absent (93), and the ketosis in the fasting state is reduced or absent in the majority of obese patients (106). Contradictory animal experiments are elucidated by the work of McKay and Sheril (77), which, unfortunately, is often misquoted. These investigators showed that fasting ketosis in the obese is variable: it is markedly decreased in all patients who present a definite endocrine history, in contrast to simple cases of obesity in which ketosis is as great or greater than in the non-obese. This would indicate that the obese endocrine patient is unable to mobilize fat rapidly in the fasting state. Contradictory findings of other investigators are explained by the fact that their material was unselected. The same explanation applies to discrepancies noted in the study of alimentary ketosis. Increased ketosis in the obese was found, especially if the fat meal was preceded by fasting or a continued low carbohydrate

diet (63, 66, 70). Our own studies, performed on 109 cases, showed the expected ketosis in all controls as well as in some endocrinopathies, but not in obese patients presenting clinical signs of pituitary insufficiency. Ketonemia was absent in 42 such cases so consistently that the "fat tolerance test" was recommended as a diagnostic aid in pituitary disease (41).

The test is based on the experimental findings that the anterior lobe secretes a "fat metabolism" hormone which is active also *in vitro* (112a). Specially prepared anterior lobe extracts elicit increase of blood ketones in the experimental animal; secretion of this pituitary factor is stimulated by ingestion of fat (2, 80). The excretion of ketone bodies in the urine after injection of pituitary extracts was first claimed by Burn and Ling (19) and their findings were corroborated by subsequent investigations (12, 20).

Ketosis is also influenced by the adrenal cortex, for but little ketosis is observed in the adrenalectomized animal fed oil or poisoned with phloridzine. A large increase in ketone bodies develops as soon as a cortical extract is administered (125).

Abnormalities of fat metabolism are also suggested by the increase in blood cholesterol which develops after adrenalectomy: the hypercholesterolemia in the adrenalectomized, as well as in the vitamin B deficient animal, can be prevented or corrected by injection of cortical extract. Intravenous injection of cortical extract in the rabbit causes a rapid drop of the blood cholesterol, which is due to the storage of cholesterol and other lipoids in the reticulo-endothelial and other cells (33, 101).

D. WATER RETENTION

The significance of water retention in obesity is generally recognized. A sudden increase in weight up to as high as 12 pounds may sometimes occur premenstrually; the rapid postmenstrual weight loss accompanied by polyuria, clearly shows the dependence of the increased weight on water retention. Even larger amounts of water are retained in some cases of allegedly simple obesity in which the gain in weight was slow and gradual. Most of the retained water stays in the intracellular compartment, although an added increase in blood volume is not uncommon. Real edema is observed only if circulatory insufficiency develops in the course of excessive obesity.

Neither the cause nor the mechanism of this water retention is clearly understood. More often than not it is concomitant with the retention of sodium chloride. Thus, water elimination may be normal if investigated by means of the Volhard test; substantial retention is demonstrable in the same patient if Zondek's salt tolerance test is performed (37, 62). Salt retention alone, however, does not adequately explain excessive hydration of the tissues in all cases—so much so that we must suspect other influences which increase the capacity of the cytoplasm to absorb abnormal amounts of water. The source of the retained water is obvious if the fluid intake of these patients is excessive, due either to unquenchable thirst or to acquired

habit. Retention is also noted in patients whose fluid intake is not above the average; it is apparently due to the marked oliguria. The urine output may be increased in the thirsty group of patients, yet it is still relatively too small to dispose of the excessive intake. In the absence of renal pathology or circulatory disturbances, the retention of water suggests hydrophilia of the tissues. The hydropexic capacity of the tissues is not uniformly increased throughout the body and may be limited to the subcutaneous fat tissue.

The influence of hormones upon the regulation of salt and water metabolism is clearly established. Some hormones increase diuresis by stimulating renal circulation while others, especially certain sterols, increase the secretory capacity of the renal cells by inducing hypertrophy of the renal epithelium. The diuretic effects of adrenalin and parathormone are especially powerful; the former is capable of overcoming the anuria of animals poisoned with uranium nitrate (53, 85, 107). Parathormone is effective through mobilization of phosphates and chlorides; it was used successfully in the anuria of nephrolithiasis or in unilateral reflex anuria following traumatic injury of the other kidney.

The renal output is small even in mild cases of hypothyroidism but increases upon administration of thyroid, particularly in myxedematous patients in which the polyuria is associated with a substantial loss of weight. The diuretic effects of thyroid medication are also apparent in simple obesity in which oliguria prevails in the absence of renal or cardiac disease.

The substantial loss of water in adrenalectomized animals or Addisonian patients can be prevented by administration of sodium chloride and/or cortical extract. The loss of water after adrenalectomy cannot be explained merely by the increased elimination; some water seems to enter and remain in the intracellular compartment. Administration of cortical sterols and especially of desoxycorticosterone, causes water retention accompanied by increased blood volume and blood pressure.

Administration of estrogen often causes water retention; this seems to explain the premenstrual gain in weight at a time when the blood estrogen level is supposed to be highest. It is still an open question whether these estrogen effects are direct or mediated through the adrenals or other endocrine glands.

The role of the pituitary in water metabolism is rather complex. The posterior lobe produces an anti-diuretic hormone, yet, subsequent to its administration, diuresis and elimination of chlorides increases. Lack of posterior lobe hormone, as in diabetes insipidus, is the cause of excessive diuresis which can be curbed by administration of posterior lobe extract. The latter is also effective in curbing thirst irrespective of its cause. Loss of water provokes secretion of the anti-diuretic hormone as shown in the adrenalectomized cat in which the anti-diuretic factor appears in the urine. Its excretion ceases upon administration of cortical extract (82).

The posterior lobe is supposed to produce "anti-diuresis" by its effect on renal function. This view is not in agreement with the observation that the hormone mobilizes sodium chloride from its depots (79, 120). Particularly significant is the increase of serum chlorides following injection of posterior lobe extract in the nephrectomized animal (84). These and other available data indicate that the posterior lobe hormone, in addition to its renal effects, acts directly on the peripheral tissues and increases their water content; as soon as this effect wears off, the retained water leaves the cytoplasm carrying along sodium chloride for subsequent elimination by the kidneys. The peripheral action of pitressin is clearly demonstrated by experiments on animals previously injected with india ink; after this blockade of the reticulo endothelial system, the posterior lobe extract causes substantial loss of water by diuresis, instead of the expected antidiuretic effects (42).

The function of the posterior lobe is closely correlated with that of other endocrine glands which regulate water metabolism; thus estrogen administration in diabetes insipidus causes sodium chloride retention and reduces the urinary volume. Even more important in the maintenance of the hormonal balance is the anterior lobe of the pituitary from which diuretic substances can be extracted (118). Conclusive evidence was offered by the observation that diabetes insipidus develops only if the pathological lesion is limited to the posterior lobe and leaves the anterior lobe undamaged. Moreover, the polyuria of such patients may subside shortly before death, if the lesion of the posterior lobe encroaches upon and destroys the anterior lobe (42). The mechanism of the anterior lobe diuresis is still controversial; the diuretic effect was supposed to be linked to the thyrotropic factor because anterior lobe extracts failed to produce diuresis in the thyroidectomized animal unless thyroxin was also given (128). Thyroidectomy, however, only reduces but does not abolish the polyuria in diabetes insipidus (26, 60).

The effects of insulin upon water retention are well known; they explain the massive gain in weight which often accompanies institution of insulin therapy in the diabetic. Polyuria and polydipsia decrease or cease simultaneously. Some of the water retention may be referable to the storage of glycogen but the amounts of water involved in this process are relatively small. It is not improbable that the hydrating effects of insulin involve the collaboration of other endocrine glands, especially the adrenals and pituitary.

This sketchy account of hormonal influences upon salt and water metabolism is in accord with clinical observations in various endocrinopathies as well as in obesity. Hypothyroidism and anterior lobe insufficiency favor water retention; similar are the effects of overactivity of the posterior lobe, the adrenal cortex and the pancreatic islands, as well as those of estrogen in large dosage. Insufficiency of the posterior lobe, though conducive to polyuria, might remain asymptomatic or actually be associated with water retention if the lesion of the pituitary involves both lobes.

The main contribution of the posterior lobe in such bilobar insufficiency is the retention of sodium chloride.

The retention of salt and water, demonstrable by the low urinary output and by the retention of test salt upon performance of the salt tolerance test, contributes to the development of obesity, not only in proportion to the actual amount of water retained. Clinical observation suggests that retention interferes with orderly function of the skin and subcutaneous tissue, for such patients are inclined to be "allergic" or susceptible to the rapid spreading of infectious processes.

E. HEREDITY AND CONSTITUTION

The theory that obesity is based on constitutional factors (7) adds another word but hardly any new knowledge to our problem, although it cannot be denied that regional accumulation of fat seems to depend on somatic influences of definitely hereditary character.

It is recognized by animal breeders that the tendency to obesity is species-linked. Detailed studies in the obese yellow mouse have shown that hereditary obesity follows Mendelian laws. Yellow mice mated with ordinary white animals, produce a litter consisting partly of yellow and partly of white mice; identical feeding of paired animals from such a litter produces quicker weight gain in the yellow mice than in the white controls. Fat accumulation was outstanding subcutaneously and intra-abdominally, especially in the female animals (22).

Studies on identical twins have shown that body weight is the most variable of the anthropometric measurements even if the twins grow up in an identical environment; the variability is greater if the environment is dissimilar, yet the differences in weight, even under the most extreme circumstances are practically negligible if compared with the average weight differences in fraternal twins or non-twin siblings; this is conclusive evidence of the decisive influence of genetic factors upon body weight (91).

Studies relative to the family background of obese patients almost always reveal that at least one of the parents is obese; moreover, marriage between an obese and a non-obese person produces children about one-half of which are obese and one-half are not (73). These repeatedly confirmed observations indicate that Mendelian laws govern the hereditary transmission of obesity. Genetic studies on a large unselected material conclusively showed that obesity is transmitted by dominant factors of which, at least, three are operative independently (23). The genetic setup varies with the species: for instance, the hereditary obesity of the yellow mouse is transmitted by a single dominant gene which simultaneously carries the yellow color.

The genes of obesity account not only for the transmission of the tendency to accumulate fat but also for the selective distribution of fat, for clinical observation has shown that fat distribution tends to be identical in mother and daughter; the close resemblance between parent and offspring was recently demonstrated by Rony (106) in 12 patients out of a group of 18. The similarity of regional fat distribution in identical

twins, even though they may differ in weight, indicates that selective deposit of fat is even more dependent on endogenous factors than body weight.

The tissues or organs which carry the genetic factors are not yet identified. Danforth (22) suggested that the ovary may be concerned in some way with the hereditary transmission of adiposity in the yellow mouse. Clinical observations favor the assumption that the hereditary transmission of obesity is linked to inherited peculiarities of the endocrine glands. Thus, many endocrinopathies are hereditary or familial. Graves' disease, hypothyroidism, various pituitary syndromes, hirsutism of the hyperinterrenal type, or hypogonadism, characterized by eunuchoid body build, quite commonly occur in parent and offspring or in several members of one family. A careful genetic study covering several generations revealed that an abnormality of the sella turcica, the so-called closed sella, is inherited on the basis of a dominant factor (114). This abnormality of the cranial bones does not necessarily entail disease or abnormal function of the pituitary, yet, the incidence of a closed sella is so great in pituitary disease that its diagnostic significance cannot be ignored.

The available evidence favors the view that hereditary transmission of obesity and particularly, of abnormal regional fat deposits, is linked to genetic factors which determine both the peculiarity of the fat tissue and the abnormality of the endocrine glands. The transmission of obesity along Mendelian lines excludes the assumption that the familial manifestation of obesity is explicable by environmental influences.

F. PRECIPITATING FACTORS

The facts marshalled in support of the view that endocrine factors influence both the regulation of energy expenditure and fat-tissue function are supported by clinical observations concerning the onset of obesity. Gain in weight is occasionally insidious and fat accumulates slowly and gradually in the course of years. In other cases, the onset is sudden or the progress of a slowly developing obesity is strikingly accelerated. Such sudden changes are observed particularly in connection with: pubescence, pregnancy, lactation, amenorrhea, menopause, impotence, and finally, convalescence from acute infections or major surgical procedures. The onset of adiposogenital dystrophy in childhood frequently follows in the wake of tonsillectomy; data suggesting a relationship between the latter and involvement of the pituitary gland were presented recently (38).

The onset of obesity is commonly associated with events pertaining to the sexual sphere; one should not ignore the possible correlation with coincident emotional changes, eating habits, or physical activity, yet the conspicuous revolution in the function of the ovary is by far more significant; participation of the pituitary and probably, of other endocrine glands, is also apparent. The changes in the incretory status, attendant to these critical periods of life, cannot remain limited to the sexual sphere without involving metabolic activities;

this is exemplified for instance by manifestation of hypermetabolism and hyperglycemia in cases of menopause and by the gratifying symptomatic response of such patients to estrogenic therapy.

The endocrine implications of the onset of obesity in convalescence are less obvious, yet they are quite clear if we recall the almost selective susceptibility of both the adrenals and hypophysis to impairment in the course of infections. Degenerative changes, circumscribed necroses or hemorrhages followed by interstitial fibrosis have been noted at autopsy (32). Such lesions subsequently may give rise to compensatory hyperplasia or formation of adenomas of either secretory or non-secretory type. Hence, the organic changes which develop in these glands in the wake of systemic infections, after massive hemorrhage, or surgical trauma might bring about either insufficiency or overactivity; these functional disturbances, through a complex chain of events, may lead to increased food intake, abnormal metabolism or both, with obesity as the eventual outcome.

According to the enumerated evidence, endocrine factors are capable of interfering along the whole line with the processes of regulation which maintain normal body weight and orderly distribution of fat deposits. Hence, disease or inadequate function of the endocrine glands assumes a weightier role in the pathogenesis of obesity, without contradicting the fact that excessive overfeeding alone may produce fat deposits if it succeeds in breaking down the compensatory mechanism of the normal body.

The frequency of frank endocrinopathies or functional endocrine disturbances in obesity is much too great to be accepted as a mere coincidence. The statement has been made, however, that obesity may be the cause of the endocrine manifestations, for endocrine symptoms such as menstrual disorders or sterility are often cured by mere weight reduction. It should be remembered before judging the merits of this argument that the careful experimental worker administers hormones in quantities proportionate to body weight. As the physiologic hormone supply of the human body obeys similar laws, it is logical to assume that the hormones secreted by e. g., the anterior lobe for the use of a body weighing 120 pounds cannot fill the requirements if the weight of the same body increases to 200 pounds or more. Such a formidable increase in obligations might easily exceed the limits of secretory adaptability. Substantial weight reduction relieves the pituitary of this extra burden and reduces hormonal requirements to a level which permits resumption of normal activities.

Another aspect of the same problem is the variable responsiveness of the peripheral fat tissue to hormonal stimulation. Metabolic disturbances incidental to the endocrinopathy may interfere radically with peripheral reactions, yet may be readily adjusted by dietary control. Thus, a mild diabetes can be controlled by diet without insulin, a response which does not contradict the pancreatic origin of the disease. It would be equally fallacious to deny the endocrine pathogenesis of

obesity because weight reduction can be accomplished by dietary means alone. Any diet so low in calories as to exceed the limits of adaptability within which energy expenditure can be curtailed, must necessarily bring about mobilization of depot fat and loss of weight. Excess fat can be disposed of, however, just as effectively without resorting to starvation diets if the endocrine factors are given due consideration. This statement is based on personal experience with a large material including patients whose previous attempts at dietary weight reduction had failed dismally whereas substantial weight loss was obtained without starvation, by suitable endocrine therapy. The abnormal regional fat distribution also yields far better to the combination of diet and endocrine treatment than to mere reduction of caloric intake.

S U M M A R Y

The reports on anatomical changes of the endocrine organs in obesity are reviewed. Their inconsistency does not permit definite conclusions.

Discussion of the data concerning the metabolic status of the obese is handicapped by the failure of previous investigators to separate "simple" and endocrine cases of obesity. Previous calculations of basal heat production were unmindful of the variable oxygen consumption attendant to anabolic processes in the cytoplasm.

Evidence is presented to show that the adipose tissue is not merely engaged in the passive storage of fat but plays an active metabolic role.

Deposit of fat is the consequence of food intake beyond the limits of the body's ability to increase energy consumption; loss of depot fat occurs if the caloric deficit is greater than the ability of the body to restrain metabolic activities. The mechanism regulating the diversified metabolic activities, including the specific dynamic action of proteins, luxury consumption and cellular anabolism, is controlled to a large extent by the endocrine glands.

The active function of the fat tissue which includes formation and storage of fat as well as its mobilization and metabolic utilization, is demonstrably under the influence of the endocrine glands.

Retention of water and salt are important contributory factors in obesity; evidence is presented indicating that salt and water metabolism is regulated by endocrine influences.

A tendency to obesity and to increased regional fat deposits is hereditary. The genetic transmission of these tendencies is frequently associated with similarly inherited peculiarities of the endocrine glands.

The onset of obesity frequently coincides with manifest changes in the activity of the endocrine system or with events likely to affect one or several endocrine organs.

Weight reduction can be accomplished by diet alone, provided the caloric intake is low enough. Better clinical results are obtained with less rigorous restriction of food intake if suitable endocrine therapy is added; regional fat deposits also yield better to such combined treatment than to mere dietary weight reduction.

R E F E R E N C E S

1. Abels, J. C., Young, N. F., Taylor, H. C. and Rhoads, C. P.: *Endocr.*, 35:213, 1944.
2. Anselmino, K. J. and K. Hoffmann: *Kl. Wschr.*, 10:2380, 1931.
3. Arndt, H. J.: *Beitr. Path. Anat.*, 79:69, 1927.
4. Arnoldi, W.: *Ztschr. Kl. Med.*, 94:268, 1922.
5. Asher, L.: *J. A. M. A.*, 108:720, 1937.
6. Barnes, B. O. and Rogoff, J. M.: *Am. J. Physiol.*, 113:21, 1935.
7. Bauer, J.: *Konst. Disposition*, Springer, Berlin, 1924.
8. Benedict, F. G. and Lee, R. C.: *Biochem. Ztschr.*, 293:405, 1937.
9. Bernhardt: *Ergeb. Inn. Med.*, 36:1, 1929.
10. Best, C. H. and Campbell, J.: *J. Physiol.*, 86:190, 1936.
11. Beznak, A. B. and Hasch, Z.: *Quart. J. Exp. Physiol.*, 27:1, 1937.
12. Black, P. T., Collip, J. B. & Thomson, D. L.: *J. Physiol.*, 82:385, 1934.
13. Blotner, H.: *Arch. Int. Med.*, 55:121, 1935.
14. Booth, G. & Strang, J. M.: *Arch. Int. Med.*, 57:533, 1936.
15. Brooks, C. Mc. & Bridge, E. M.: *Endocr.*, 35:208, 1944.
16. Bruch, H.: *Amer. J. Dis. Child.*, 58:1001, 1939.
17. Bruch, H.: *Amer. J. Dis. Child.*, 59:739, 1940.
18. Bulstao, E. & Carlson, A. J.: *Am. J. Physiol.*, 69:107, 1924.
19. Burn, J. H. & Ling, H. W.: *J. Physiol.*, 69:XIX, 1930.
20. Butts, J. S., Cutler, C. H. & Deuel, H. J.: *J. Biol. Chem.*, 106:45, 1934.
21. Conn, J. W.: *Physiol. Revue*, 24:31, 1944.
22. Cushing, H.: *Bull. Johns Hopk. Hosp.*, 50:137, 1932.
23. Danforth: *J. Heredity*, 18:153, 1927.
24. Davenport, C. H.: *Carnegie Inst. Wash., Publ. No. 329*, 1925.
25. Eger, W.: *Kl. Wschr.*, 17:1033, 1938.
26. Engelbach, W.: *Endocrine Medicine*, Thomas, Springfield, 1932.
27. Findley, T.: *Ann. Int. Med.*, 11:701, 1937.
28. Foster, G. L. & Smith, P. E.: *J. A. M. A.*, 87:2151, 1926.
29. Fryberg, R. H. & Newburgh, L. H.: *Arch. Int. Med.*, 58:229, 1936.
30. Frykman, H. M.: *Endocr.*, 31:23, 1942.
31. Fulton, M. N. & Cushing, H.: *Arch. Int. Med.*, 50:649, 1932.
32. Gestler, H.: *Deutsch. Arch. Kl. Med.*, 157:36, 1927.
33. Goldzieher, M. A.: *The Endocrine Glands*, D. Appleton Co., New York, 1939.
34. Goldzieher, M. A.: *Verhandl. Deutsch. Path. Ges.*, 24:286, 1929.
35. Goldzieher, M. A.: *Ann. Res. Nerv. Ment. Dis.*, 17:536, 1938.
36. Goldzieher, M. A.: *Endocr.*, 20:86, 1936.
37. Goldzieher, M. A.: *Clinics*, 1:1069, 1943.
38. Goldzieher, M. A.: *South. Med. & Surg.*, 106:No. 2, 1944.
39. Goldzieher, M. A. & Gordon, M. B.: *Endocr.*, 17:569, 1933.
40. Goldzieher, M. A. & Hirschhorn, L.: *Arch. Path.*, 4:958, 1927.
41. Goldzieher, M. A., Sherman, I. & Alperstein, B.: *Endocr.*, 18:505, 1934.
42. Goldzieher, M. A. & Kaldor, J.: *Ztschr. Ges. Exp. Med.*, 76:819, 1931.
43. Goldzieher, M. A. & Koster, H.: *Am. J. Surg.*, 27:93, 1935.
44. Goldzieher, M. A., Reimer, N. & Goldzieher, J. W.: *Am. J. Dig. Dis.*, 12:387, 1945.
45. Gordon, E. S., Sevringhaus, E. & Stark, M. S.: *Endocr.*, 22:45, 1938.
46. Grafe, E.: *Krankheiten d. Stoffwechsels*, Springer, Berlin, 1931.
47. Gudernatsch, F.: *Anat. Rec.*, 11:357, 1917.
48. Hagedorn, H. C., Holton, C. & Johansen, A. H.: *Arch. Int. Med.*, 40:30, 1927.
49. v. Harn, F.: *Frankf. Ztschr. f. Path.*, 21:337, 1918.
50. Hausberger, F. X. & Gujot, O.: *Arch. Exp. Path. u. Pharm.*, 187:647, 1935.
51. Heinbecker, P.: *Medicine*, 23:225, 1944.
52. Heinbecker, P. & White, H. L.: *Proc. Soc. Exp. Med.*, 49:324, 1944.
53. Hess, L. & Wiesel, J.: *Wien. Kl. Wschr.*, 26:317, 1913.
54. Hetenyi, G.: *Deutsch. Arch. Kl. Med.*, 179:134, 1936.
55. Hetherington, A. W. & Ranson, S. W.: *Endocr.*, 31:30, 1942.
56. Hoffmann, E.: *Ztschr. f. Dermatologie*, 22:558, 1915.
57. Hoffmann, A. & Wertheimer, E.: *Pflueg. Arch.*, 217, 728, 1927.
58. Hoskins, R. G. & Freeman, H.: *Endocr.*, 17:29, 1933.
59. Housay, B. A.: *Endocr.*, 18:409, 1932.
60. Ingram, W. R. & Fisher, C.: *Endocr.*, 21:373, 1937.
61. Johnston, M. W.: *Jnl. Cl. Invest.*, 11:437, 1932.
62. Kahlmeter, G.: *Acta Med. Scand.*, 75:107, 1931.

63. Keeney, E. L., Sherril, J. W. & MacKay, E. M.: *Am. J. Dig. Dis.*, 3:23, 1936.
64. Kraus, J. E.: *Kl. Wschr.*, 13:487, 1934.
65. Kraus, J. E.: *Kl. Wschr.*, 16:1528, 1937.
66. Kugelman, B.: *Ztschr. f. Kl. Med.*, 115:454, 1931.
67. Kup, J.: *Endokrinologie*, 6:102, 1930.
68. Kure, O. & Okinaka: *Kl. Wschr.*, 16:1789, 1937.
69. Lee, M. & Ayres, G. B.: *Endocr.*, 20:489, 1936.
70. Leites, S. M.: *Acta Med. Scand.*, 89:199, 1936.
71. Leschke, E.: *Handb. der Inneren Sekretion, Kabitzsch, Leipzig*, 1928, Vol. 3.
72. Levietes, P. H.: *J. Cl. Invest.*, 14:57, 1935.
73. Liebendorfer: *Arch. f. Rassenbiolog.*, 15:18, 1923.
74. Liebesny, P.: *Biochem. Ztschr.*, 144:308, 1924.
75. Loew, A. & Krcma, A.: *Kl. Wschr.*, 11:584, 1932.
76. MacKay, E. M. & Barnes, R. H.: *Am. J. Physiol.*, 118:184, 1937.
77. MacKay, E. M. & Sherril, J. W.: *Endocr.*, 21:677, 1937.
78. McKinley, E. B. & Fisher, N. F.: *Am. J. Physiol.*, 76:269, 1926.
79. McQuarrie, I., Thompson, W. H. & Ziegler, M. R.: *J. Pediat.*, 8:277, 1936.
80. Magistris, H.: *Endokrinologie*, 11:176, 1932.
81. Mark, R.: *Ztschr. f. Arbeitsphys.*, 2:129, 1929.
82. Martin, S. T., Herlich, W. C. & Fazekas, J. F.: *Am. J. Physiol.*, 127:50, 1939.
83. Mirski, A., Rosenbaum, T., Stein, L. & Wertheimer, E.: *J. Physiol.*, 92:48, 1938.
84. Miura: *Arch. Exp. Path. Pharm.*, 107:1, 1925.
85. Molnar, B.: *Orvosi Hetilap*, 48:387, 1904.
86. Mulinos, M. & Pomerantz, L.: *Endocr.*, 29:558, 1941.
87. Myerson, A.: *Am. J. Psychiat.*, 93:263, 1936.
88. Newburgh, L. H. & Johnston, L. W.: *Med. Clinics North America*, 27:327, 1943.
89. Newburgh, L. H., Johnston, M. W., Lashmet, F. H. & Sheldon, J. M.: *J. Nutr.*, 13:203, 1937.
90. Newburgh, L. H., Wiley, F. H. & Lashmet, F. H.: *J. Cl. Invest.*, 10:703, 1931.
91. Newman, H. H., Freeman, F. N. & Holzinger, K. J.: *Twins, University Press, Chicago*, 1937.
92. O'Donovan, D. K. & Collip, J. B.: *Endocr.*, 23:778, 1938.
93. Paschkis, K. & Butru, G. D.: *Ztschr. Kl. Med.*, 125:654, 1933.
94. Plaut, R.: *Deutsch. Arch. Kl. Med.*, 139:285, 1922.
95. Putnam, T. J., Benedict, E. B. & Teel, H. M.: *Arch. Surg.*, 18:1708, 1929.
96. Raab, W.: *Kl. Wschr.*, 13:281, 1934.
97. Reed, L. L., Anderson, W. E. & Mendel, L. B.: *J. Biol. Chem.*, 87:147, 1930.
98. Reifenstein, E. C., Forbes, A. P., Kinsell, L. W. & Albright, F.: *Endocr.*, 35:213, 1944.
99. Reiss, M., Epstein, Fleischmann, F. & Schwarz, L.: *Endokrinologie*, 17:302, 1936.
100. Reiss, M., Balint, Oesterreicher & Aronson: *Endokrinologie*, 18:1, 1936.
101. Reiss, M., Winter, K. A. & Valdecass, S.: *Endokrinologie*, 11:97, 1932.
102. Riddle, O. & Bates, R. W.: *Assn. for Res. Nerv. Ment. Dis.*, 17:287, 1938.
103. Richardson, H. B.: *Endocr.*, 35:208, 1944.
104. Richter, C. P.: *Endocr.*, 29:115, 1941.
105. Richter, C. P. & Birmingham, J. R.: *Endocr.*, 29:655, 1941.
106. Rony, H.: *Obesity and Leanness, Lea & Febiger, Phila.*, 1946.
107. Roth, W. & Bloss: *Virch. Arch.*, 238:325, 1922.
108. Rowe, A. W.: *Endocr.*, 13:327, 1929.
109. Schilling, W. & Laqueur, G. L.: *Endocr.*, 39:103, 1931.
110. Schur, H. & Loew, A.: *Wien. Kl. Wschr.*, 41:225, 1928.
111. Scoz, G., Baer, B. & Boeri, E.: *Arch. di Sc. Biol.*, 22:142, 1936.
112. Shelling, D. H.: *The Parathyroids, C. V. Mosby Co., St. Louis*, 1935.
- 112a. Shipley, R. A.: *Am. J. Physiol.*, 141:662, 1944.
113. Smith, P. E.: *Endocr.*, 7:579, 1913.
114. Snyder, L. H. & Blank, F.: *Ohio St. Med. Jnl.*, 40:318, 1944.
115. Soskin, S.: *Endocr.*, 26:297, 1940.
116. Strandberg, J.: *Ztschr. f. Dermatologie*, 22:556, 1915.
117. Strouse, S., Saunders, A. D. & Wang, C. C.: *Arch. Int. Med.*, 36:397, 1925.
118. Teel, H. M.: *J. A. M. A.*, 93:760, 1929.
119. Tuerkischer, E. & Wertheimer, E.: *J. Physiol.*, 100:385, 1942.
120. Unna, K. & Walterskirchen, L.: *Arch. Exp. Path. Pharm.*, 181:681, 1936.
121. Verzar, F. & Laszt, E.: *Biochem. Ztschr.*, 288:356, 1936.
122. Viegas: *Brazil Medico*, 2:920, 1935.
123. Walters, W., Wilder, R. M. & Kepler, E. J.: *Ann. Surg.*, 100:670, 1934.
124. Wells, H. G.: *J. A. M. A.*, 114:2177, 1940.
125. Wells, B. B. & Kendall, E. C.: *Proc. Mayo Clinic*, 16:113, 1941.
126. Wertheimer, E.: *Pflueg. Arch.*, 219:190, 1928.
127. Whipple, G. H. & Madden, S. C.: *Medicine*, 23:215, 1944.
128. White, F. & Heinbecker, P.: *Am. J. Physiol.*, 118:276, 1937.
129. Zeynek, E.: *Frankf. Ztschr. Path.*, 44:387, 1933.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
*J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

* With the Armed Forces.

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

CLINICAL MEDICINE

MOUTH AND ESOPHAGUS

TOMLINSON, W. F. AND WILSON, T. A.: *Esophageal carcinoma in British West Indian and Panamanian Negroes.* (Arch. Path., v. 39, p. 79, Feb. 1945).

Esophageal carcinomas to the extent of less than 1% in 591 women and 2.3% in 1564 men were found in negroes at autopsy. Carcinomas in general were found in 197 of the men and 80 of the women. The esophageal carcinomas thus constituted 17.7% and 6.3% respectively of the carcinomas in both sexes. In the male only gastric carcinoma and prostatic carcinoma exceeded esophageal carcinoma in frequency. Syphilis had a high correlation with the esophageal carcinomas; 52% of the autopsy cases with these carcinomas had syphilis as compared with 8.7% in the general negro autopsy population. — G. Klenner.

BAUER, W. H. AND FOX, R. A.: *Adenomyoepithelioma (cylindroma) of palatal mucous glands.* (Arch. Path., v. 39, p. 96, Feb. 1945).

Tumors of the palate were studied microscopically in 6 cases. Although designated as "cylindroma" the tumors actually were associated with the parenchyma more than with the hyalinized stroma cylinders. The authors emphasize the proliferation of the myoepithelial cells of the intercalated ducts. These myoepithelial or basket cells form a stroma or strands arranged in adenomatous patterns. The hyalin substance is formed by conversion of the fibrous stroma under the influence of substances from the secreting cells. The fibrous wall is the source of the branching fibrous stroma in the aggregations of epithelium. The authors suggest that the palatal tumors, which are not adenocarcinoma or "mixed tumors", should be designated as "adenomyoepithelioma." While it is non-cancerous, the tumor may become malignant. — G. Klenner.

KINI, M. G.: *Epitheliomas of the palate caused by smoking of cigars with the lighted end inside the mouth.* (Indian Med. Gaz., v. 79, p. 572, 1944).

Cancer of the palate is common in the Northern Circars. Investigation showed a peculiar habit of smoking with the lighted end inside the mouth. The epithelial lining of the palate undergoes leucoplakic changes at the site where the lighted end lies in juxtaposition.

Irregularly oval or crescentic ulcers develop which may undergo malignant change of the nodular or ulcerative type. On histopathologic examination they have proved to be true epitheliomas of the squamous type. From the recorded evidence, it takes a long time for the cancer to develop. Children of 6-7 years begin to acquire this habit and the average age when the cancer shows is 42.5 years. — Courtesy Biological Abstracts.

BOWEL

BARKER, C. S.: *Acute colitis resulting from soapsuds enema.* (Canadian Med. Assoc. J., v. 52, p. 285, March 1945).

Immediately after taking a soapsuds enema the patient, a woman, experienced cramp-like pains in the lower left abdomen and a sense of weakness in the limbs. Serosanguinous fluid was passed. Large quantities of bloody fluid were removed from the rectum next day. Roentgenographic evidence of an extremely irritable and spastic colon was obtained on a barium enema. Hot abdominal compresses, a low residue diet and sedatives were used until the patient recovered. The patient gave a negative reaction to a patch test with soap. — G. Klenner.

LIVER AND GALLBLADDER

GILLMAN, J., GILLMAN, T. AND BRENNER, S.: *Vitamin A and porphyrin-like fluorescence in the livers of pellagrins, with special reference to the effects of a high carbohydrate diet and methionine.* (South African J. Med. Sci., v. 10, p. 67, Sept. 1945).

In 60 adult and infant pellagrins 109 liver fragments were removed by biopsy and examined by fluorescence microscopy. In very fatty livers the vitamin A content of Kupffer cells was sharply reduced. There is a reciprocal relationship between the amount of fat in the liver and the amount of Vitamin A fluorescence in the Kupffer cells. The amount of fluorescence in the liver cells was greatly reduced in more than half of the cases examined. During the formative stages of the fat the fat globules in the liver cells tended to fluoresce constantly. During fat resorption the fluorescence decreased.

A red porphyrin-like fluorescence was noted in liver cells in cases where iron pigment was being actively deposited.

deposited. No vitamin A fluorescence could be noted in these regions.

Administration of large amounts of vitamin A together with a full diet did not result in as great an increase in storage of the vitamin by the liver as did administration of ventriculin in the same diet. Vitamin A in conjunction with the full diet aggravated the disease.

The fatty livers of two infant pellagrins did not respond to methionine. The fat was absorbed after treatment with ventriculin.—M. H. F. Friedman.

MAN, E. B., KANTIN, B. L., DURLACHER, S. H. AND PETERS, J. P.: *The lipids of serum and liver in patients with hepatic disease.* (*J. Clin. Invest.*, v. 24, p. 263, Sept., 1945).

The serum lipids were determined in patients with diseases of the liver and pancreas, and biliary tract obstruction. The lipids were fractionated into their major components in order to determine the extent of variations of each. Samples of liver secured at autopsy were also investigated.

In 70 patients with liver or bile duct disease determinations of liver lipids were carried out on 174 occasions. During biliary obstruction the total cholesterol and lipid phosphorus are elevated in the sera but return to normal when the obstruction is relieved. These fractions are also high in the sera of patients with liver cirrhosis or infectious hepatitis. Hyperlipemia is probably a product of biliary obstruction.

In patients with portal cirrhosis the cholesterol and lipid phosphorus are normal or subnormal and these fall as the disease progresses. In patients with liver hepatitis and in some patients with infectious hepatitis these lipid fractions are also low. Hypolipemia may be the result of extensive degeneration or destruction of the liver parenchyma. Neutral fat is seldom elevated in liver disease but in obstructive icterus and infectious hepatitis it may be greatly elevated but falls again when the obstruction is relieved or the hepatitis subsides.

The ratio of free to total cholesterol is most frequently disturbed in liver disease. In liver disease the ratio of phospholipids to cholesterol is greater than normal, particularly when there is a hyperlipemia. No definite beneficial effects were observed in a series of patients with various hepatic diseases who were given cholin chloride and other lipotropic substances.—M. H. F. Friedman.

ULCER

HINTON, J. W.: *Subtotal gastrectomy in medically resistant ulcer.* (*N. Y. State J. Med.*, v. 45, p. 291, Feb., 1945).

Surgical intervention in ulcer should be carefully restricted. Operation should not be performed on patients who do not obey orders about dietary regimen. Hemorrhage from an ulcer in itself is not an indication for surgery, particularly if the patient is under 45 years of age and the hemorrhage can be otherwise controlled and the patient does not suffer severe pain.

While penetrating ulcers should receive surgical attention, this should not be carried out on the basis of roentgenologic diagnosis alone. Pyloric stenosis in the absence of pain is likewise not an indication for surgery. Surgery should be applied to cases with uncontrolled pain, to cases with pyloric stenosis due to a previous operation, to cases with profuse bleeding if they are over 45 years old, and to true perforating ulcer cases. The site of anastomosis of the remaining portion of the stomach to the intestine should be chosen with care. The pylorus and duodenal cap should be removed when subtotal gastrectomy is performed.—I. M. Theoné.

SURGERY

ABLAIEVA, I. S.: *Surgical treatment of prolapsus recti in children after the method of Thiersch.* (*Pediat.*, (Moscow), 1944, p. 29, 1944).

Between 1940-43, 44 cases of rectal prolapse were treated in the hospital. Dysentery was the cause of the prolapse in 15 cases; chronic diarrhea in 11 cases; it developed in 5 cases after whooping cough; it followed pneumonia and other infectious diseases in 10 cases. Operation was performed in 35 cases, the method of Thiersch being used in all cases except that a thick silk thread was used instead of a wire (wire was found to cause ugly scars and fistulas). After cleansing the lower bowel with enemas, with ether as an anesthetic, incisions of about 2-3 mm. length were made about 1 cm. laterally from the anal orifice. A silk string was then introduced with a Dechamps needle and led around the anus; under the control of an assistant's finger introduced into the anus the silk thread was tied and then the incisions sutured with catgut. No complications were seen to arise in most of the cases. A mild relapse occurred in one case which is reported. In some of the cases, abscesses did develop and the silk thread had to be removed through the fistula which developed. No further trouble occurred. There were 3 deaths. Other methods of both conservative and surgical treatment of rectal prolapse are described and discussed and the Thiersch operation recommended as the simplest surgical intervention in cases which have failed to respond to conservative treatment.—Courtesy Biological Abstracts.

JARBOE, J. P. AND PRATT, J. H.: *Perforated gastric carcinoma treated by resection: report of case.* (*Proc. Staff Meet. Mayo Clinic*, v. 20, p. 446, Nov., 1945).

Perforation of a gastric carcinoma occurred 22 days before operation. Penicillin, 120,000 units, and sulfadiazine, 90 grains, were given daily: at operation a large abscess was found involving the stomach and the left lobe of the liver and extending to the diaphragm. An adenocarcinoma was present in the distal third of the stomach. About 70% of the stomach was resected and gastrojejunostomy performed. Fifteen grams crystalline sulfathiazole was placed in the peritoneal cavity. Convalescence was uneventful.

The authors emphasize that the sulfadiazine and

penicillin inhibited development of complications that usually follow such operations so late after perforation. They believe that these two drugs permit more radical surgical procedures than were formerly believed possible. — M. H. F. Friedman.

EXPERIMENTAL MEDICINE

SECRETION

HOLLANDER, F.: *Physiology of mucus secretion*. (*J. Nat. Cancer Inst.*, v. 5, p. 367, April, 1945).

Various substances were applied to the mucosa of gastric corpus pouches when they were not secreting acid. These substances so applied resulted in the secretion of mucus. Clove oil gave mucus which had a peak pH around 8.4 whereas other substances, including 50-85% alcohol and saturated solutions of ether, produced a mucus which had a peak pH around 7. This was taken to indicate that the various irritants resulted in a secretion of mucus and in formation of a transudate and inflammatory transudate, the latter process being least with clove oil.

Smears of mucus showed microscopically various cells and crystalline materials. Columnar cells were present in large numbers. Mucus which is little contaminated by exudate has a buffer capacity as high as 84 milliequivalents and a chloride concentration between 57 and 186 milliequivalents. Neither the buffer capacity nor the chloride content of the mucus could be correlated with the pH values. — M. H. F. Friedman.

ABSORPTION

LEONARDS, J. R. AND FREE, A. H.: *A note on gastric retention in one-hour, two-dose glucose tolerance tests*. (*J. Lab. Clin. Med.*, v. 30, p. 1070, December, 1945).

The Exton-Rose test consists of giving the subject two 50 gram doses of dextrose thirty minutes apart and determining the blood sugar level at 0, 30, and 60 minutes. This test is being used in many clinics in the belief that it is more accurate than the single dextrose test.

Leonards and Free performed the test on 16 normal men. After 60 minutes they withdrew the stomach contents and analyzed for dextrose. From 38 to 62 grams dextrose (average 50 grams) were recovered from the stomach. Consequently the authors question the advantage gained by the administration of the second dose of dextrose, since the stomach retains a similar amount and makes it unavailable for absorption during the test period. — M. H. F. Friedman.

HAZLETON, T. W. AND GODFREY, E. A. M.: *Absorption of single doses of iron*. (*J. Pharmacol. Exper. Therap.*, v. 83, p. 158, February, 1945).

Ferric ammonium citrate is less irritating to the intestinal tract than is iron sulfate. Both forms of iron may be absorbed with effective results without producing irritation. Absorption from the intestine begins immediately after introduction and is rapid, though

not complete until about six hours. The presence or absence of food was not found to be a determining factor for absorption nor was the question of fatigue. The citrated iron was absorbed more rapidly in the males while the iron sulfate was taken up more rapidly in the females. The amount absorbed after a single dose was as great as that following administration of the iron in divided doses. — B. R. Adolph, Jr.

PATHOLOGY

LOWRY, J. V., ASHBUM, L. L. AND SEBRELL, W. H.: *Treatment of experimental liver cirrhosis*. (*Quart. J. Studies Alcohol*, v. 6, p. 271, December, 1945).

Albino rats were kept on a diet which results in development of liver cirrhosis. In addition the animals were given 20% ethyl alcohol instead of water as their source of fluid. Animals on this diet live to a maximum of 113 days. After 63 to 84 days on the diet the animals were subjected to laparotomy and sections of liver were removed for study. Subsequently the animals were kept on the same diet but were treated by daily administration of large amounts of choline chloride or were given an additional diet high in casein.

During the period of treatment the gross and microscopic appearance of the liver were greatly improved. Therapy prevented further progression of the cirrhotic process although there was no effect on the fibrous tissue present. The histological picture of the parenchyma was greatly improved. — I. H. Dougherty.

COS, A. J. AND BARNES, V. R.: *Experimental hyperplasia of the stomach mucosa*. (*Proc. Soc. Exper. Biol. Med.*, v. 60, p. 118, October, 1945).

Guinea pigs were injected intramuscularly 3 times a week with 3 to 6 mg. histamine phosphate. The animals were sacrificed after 2 to 4 weeks of treatment and the number of parietal cells in the entire stomach estimated from examination of representative standard sections.

When the total estimated number of parietal cells were plotted against the body weight of the animal it was found that the histamine-treated animals had a greater number of parietal cells than the control animals. The authors believe this was due to true hyperplasia and the result of protracted stimulation of acid gastric secretion with histamine over a period of 2 to 4 weeks. — M. H. F. Friedman.

FIELD, J. B., BAUMANN, C. A. AND FINK, K. P.: *Prothrombin activity in rats with hepatic and other tumors*. (*Cancer Res.*, v. 4, p. 768, December, 1944).

Prothrombin time on 12.5% plasma was determined in rats with spontaneous tumors, induced tumors or inoculated Flexner-Tobling tumors. No prolongation was found as compared with normal rats of the control series. However, a mild hypoprothrombinemia was found in rats with primary hepatic tumors. The extent and duration of the low prothrombin were in-

fluenced by the relative amount of normal liver tissue. Vitamin K had little or no influence on the hypoprothrombinemia in rats with hepatic tumors.—N. M. Small.

PATHOLOGICAL CHEMISTRY

RECANT, T., CHARGUFF, E. AND HANGER, F. M.: *Comparison of the cephalin cholesterol flocculation with the thymol turbidity test.* (*Proc. Soc. Exper. Biol. Med.*, v. 60, p 245, November, 1945).

This study indicates that the mechanisms responsible for the positive reactions in the thymol turbidity test and cephalin flocculation test are different. While the thymol test is generally positive in those hepatic diseases which also yield positive cephalin-cholesterol flocculation tests, certain exceptions are notable, such as biliary cirrhosis and convalescent hepatitis.

Fundamental differences in the mechanisms of the two tests are shown when the effects of sodium chloride and lipid material are studied, as well as the reactions obtained on sera which have been separated by electrophoresis or by ultracentrifugation. All thymol turbidity tests become negative if sodium chloride is included in the system: on the other hand the presence of saline has no effect on the development of the flocculation reaction. The presence of lipids is essential for the thymol reaction but not for the cephalin flocculation reaction. Thymol-positive sera became negative if the lipids are extracted with ether, and became positive again on the addition of cephalin, crude lecithin, or cholesterol. Albumin and gamma globulin fractions obtained by electrophoretic separation of sera give negative thymol tests while the gamma globulin gives positive cephalin flocculation tests. Sera separated by ultracentrifugation showed that the positive thymol reaction was obtained with different layers than the flocculation reaction, depending on the source of the sera.—M. H. F. Friedman.

DICK, A.: *The cephalin-cholesterol flocculation reaction as a test of hepatic function.* (*Brit. Med. J.*, p. 182, February, 1945).

The cephalin-cholesterol flocculation reaction was studied in 100 normal healthy subjects, 74 subjects with either hepatic or biliary tract disease, and 164 subjects with various ailments which were not hepatic or biliary in nature. The author found that the sera from the healthy subjects gave negative readings at 24 hours. However, if the sera were read at 48 hours the results were 13% positive. Consequently readings should be made at 24 hours and not later. All cases of infective hepatitis and almost no cases of obstructive jaundice gave positive flocculation reactions, the degree of flocculation being in proportion to the severity of the liver disease. In hepatic cirrhosis and arsenical hepatitis the tests were positive in about 33% and 66% of the cases respectively.—F. E. St. George.

METABOLISM and NUTRITION

AYKROID, W. R. AND GAPALON, C.: *Nutritional diarrhea.* (*Ind. Med. Gaz.*, v. 80, p. 88, February, 1945).

The study was made on 54 patients in the Stanley Hospital in Madras. Chronic noninfective diarrhea without fatty stool was observed more frequently in females than in males. The patients had all subsisted on poor diets of rice. Improvement was striking in most cases when nicotinic acid was given intramuscularly, but it was effective only in mild cases of diarrhea when given orally. On returning to their homes and their poor diets of rice the patients would suffer a relapse within a few months. Associated with this nicotinic acid deficiency type of nutritional diarrhea were microcytic anemia, glossitis and hypochlorhydria or even achlorhydria.—F. X. Chockley.

SOKAL, H. B.: *Effects of some liver extracts on the carbohydrate metabolism.* (*Arch. Intern. Med.*, v. 75, p. 324, 1945).

Liver extracts were administered to groups of normal rats. Some of the extracts resulted in glycogenolysis, hyperglycemia and glycosuria. Apparently a factor is present in these liver extracts which is responsible for these effects on carbohydrate metabolism. The factor is water-soluble, heat stable, dialyzable; it is not a protein and is not identical with the antianemic principle. The extracts are more potent on parental than oral administration.—G. N. N. Smith.

ELLINGER, P., COULSON, R. A. AND BENESCH, R.: *Production and release of nicotinamide by the intestinal flora in man.* (*Nature*, v. 154, p. 270, 1944).

A considerable discrepancy occurs between the daily elimination of nicotinamide methochloride in healthy human beings and their daily intake of nicotinamide of current diets. "Sterilization" of the alimentary tract with sulfaguanidine resulted in a marked drop in the nicotinamide methochloride elimination. Succinylsulfathiazole likewise produced a sharp drop in normal and chronic pellagrins, whereas sulfathiazole caused no significant change and absence did not interfere with the nicotinamide metabolism. Nicotinamide given at the end of the dosing period produced the usual rise in methochloride elimination. The responses to nicotinamide administration were lower with oral doses than with subcutaneous injection. Thus a synthesis and release of the vitamin by the intestinal flora normally takes place; this mechanism is impaired by bacteriostatic agents; and the gap between the dietary intake and elimination of nicotinamide appears to be filled by nicotinamide produced and released by intestinal flora. The primary effect of milk and maize on the intestinal flora is discussed.—Courtesy Biological Abstracts.

Protein Deficiency in Man

By

MELVILLE SAHYUN, Ph. D.

DETROIT, MICHIGAN

MALNUTRITION results from inadequate intake not only of proteins but also of other foodstuffs such as fats and carbohydrates, of essential minerals, and of dietary factors such as vitamins. It becomes particularly widespread with decreased natural resources of foodstuffs brought about by wars or by economic conditions. The term "malnutrition" is quite general and covers all kinds of dietary deficiencies. Protein deficiency is demonstrable not only among undernourished but among well-to-do individuals who, for some reason or another, have neglected their dietary requirements of proteins and accessory factors.

So that we may fully appreciate the clinical significance of proteins and their degradation products, the amino acids, in disease, we must have a basic understanding of their nutritional importance in health. The following table is based on the 1942 recommendation of the Food and Nutrition Board of the National Research Council.

TABLE I

*Daily protein and caloric allowances as recommended by the Food and Nutrition Board of the National Research Council, in 1942**

	Protein Grams	Calories
Children		
1 - 3 years	40	1200
4 - 6 years	50	1600
7 - 9 years	60	2000
10 - 12 years	70	2500
13 - 15 years (girls)	80	2800
13 - 15 years (boys)	85	3200
16 - 20 years (girls)	75	2400
16 - 20 years (boys)	100	3800
Man (70 Kg.) Sedentary	70	2500
" Moderately active	70	3000
" Very active	70	4500
Woman (56 Kg.) Sedentary	60	2100
" Moderately active	60	2500
" Very active	60	3000
" In pregnancy (latter half)	85	2500
" Lactation	100	3000

*Sherman, Henry C.: The Science of Nutrition. New York: Columbia University Press, 1943.

Infancy and Adolescence. Protein requirements in infancy and adolescence are much higher than in adulthood. This is obvious as proteins are needed not only for tissue repair and maintenance but for growth. Infants up to the age of one year require as much as 3 to 4 grams of protein per kilogram of body weight. Since human milk is considered an ideal diet for infants, it may be worthwhile to compare its composition with that of cow's milk.

Frederick Stearns and Company Division, Sterling Drug Inc., Detroit 31, Michigan.

TABLE II
Composition of human and cow's milk

	Human Milk	Cow's Milk
Water	87.5	87.0
Protein	1.5	3.5
Fat	3.0	4.0
Milk sugar (Lactose)	7.5	5.0
Mineral matter (Ash)	0.2	0.5

An analysis of the composition of human milk indicates the ratio of 1 for protein, 2 for fats and 5 for carbohydrates. On the basis of 3 grams of protein per kilogram of body weight, the daily requirements of the primary foodstuffs and the caloric intake of an infant weighing 7 kilograms would be as follows:

TABLE III
General diet for a 7 kg. infant

	Per kg.	Total Intake
Protein	3	21 grams
Fats	6	42 grams
Carbohydrates	15	105 grams
Calories	126	882

During adolescence there is also a demand for high protein as well as for high caloric intake. Girls and boys up to the age of 20 require a high protein allowance per kilogram of body weight for growth as well as for maintenance. Their need for fats and carbohydrates is likewise high to allow for greater activity.

Adulthood and Old Age. Man's protein requirement after the age of 20 becomes fairly constant. However, his caloric intake varies with his activity. For moderately active and very active men provision has been made (see Table I) for higher caloric intake by increasing the allowance of fats and carbohydrates.

Man's protein requirement in old age is not fully established. Some are of the opinion that owing to physiological changes the daily protein allowance should be less than during adulthood, as in old age man may have defective or absent teeth, inadequate gastric and pancreatic secretions, impaired absorption, constipation, and other physiological disorders. Under the circumstances, if he cannot tolerate the ingestion of a sufficient amount of proteins for the maintenance of nitrogen balance, semi-digested proteins or a complete amino-acid mixture should be administered to prevent nitrogen deficit.

PROTEIN DEFICIENCY

The early symptom of protein deficiency is negative nitrogen balance. Other physiological disorders which are also attributable to protein deficiency are: (1) *Hypoproteinemia*, (2) *Infections*, (3) *Edema*, and (4) *Nutritional Anemia*. In this connection it is interesting

to note the recent report of Magee in the British Medical Journal. He stated that failure in absorption is the essential lesion in starvation. Progressive decline in the efficiency of absorption increases with fasting time, due to a decline in the functional efficiency of the epithelium of the small intestine. There also occurs a slowness of the metabolic functions of the body. By prolonged fasting or famine the essential cells of the small intestinal walls are destroyed so that the oral administration of food at this stage is harmful and acts as an irritant, causing diarrhea and dehydration. The first step in the treatment of starvation should be to restore the structure and functions of the intestinal epithelium. This is best done by parenteral administration of amino acids and glucose, along with vitamins.

One of the functions of the intestinal epithelium is to protect the body against infections, particularly against microorganisms that are present in the food. This in Magee's opinion explains the frequent occurrence of ulcers in the gastrointestinal tract.

1. *Hypoproteinemia.* The early stages of protein deficiency are not readily recognizable by simple laboratory diagnostic procedures. Values for hemoglobin and plasma proteins may still be within the normal range. The only accurate measure is that of nitrogen balance studies. These studies should be made for several days under well-controlled conditions. Should they indicate a negative nitrogen balance, protein deficiency is evident and immediate steps must be taken to correct it and to bring about at least nitrogen equilibrium. Thus protein deficiency may exist in an individual without being accompanied by hypoproteinemia. A loss of $2\frac{1}{2}$ grams of nitrogen a day represents a loss of 15 to 16 grams of protein or approximately 100 grams of tissue. Negative nitrogen balance is accompanied by loss of appetite, loss of weight and a general feeling of fatigue. When individuals have reached this stage they become alarmed at their condition and quite often attempt self-medication. Since plasma protein represents the albumin and globulin content of blood, and the latter is about seven per cent of the body weight, a moderate loss in body weight need not be demonstrable with low plasma protein. On the other hand, a decrease in the true value of plasma protein content of blood is of considerable clinical significance. Be it understood that protein is not stored in the body in the sense that fats and carbohydrates are. The protein content of plasma is in constant, dynamic equilibrium with tissue proteins. Thus it is obvious that when the true plasma protein content is low there is protein deficiency.

The term "true plasma protein" is used to denote the actual protein content of plasma when normal blood volume has been computed. Normal individuals may show "apparent" hypoproteinemia with increased blood volume. On the other hand, hypoproteinemic individuals may show "apparent" normal values for plasma protein with decreased blood volume.

2. *Infections.* True hypoproteinemia is an advanced stage of protein deficiency and well indicates that not only is the serum protein level considerably below normal but tissue proteins, or as some have termed them,

"reserve proteins", have suffered considerable losses.

The two major types of serum protein are albumins and globulins. Observers in this field are of the opinion that the first effect of hypoproteinemia is a lowering of the albumin fraction. Serum albumin is chiefly concerned with the maintenance of the colloidal osmotic pressure of blood. Therefore a decrease in the serum albumin level brings about an alteration in the colloidal osmotic pressure system of blood, giving rise to nutritional edema and a general disturbance of tissue permeability. This has been noted by numerous investigators and particularly by those interested in hypoproteinemia and gastrointestinal diseases. Edema of the gastric wall surrounding the stoma has been reported. Others have also observed a general disturbance in the water balance system as well. This may well account for poor absorption of essential dietary factors and minerals through the gastrointestinal tract.

Prolonged protein deficiency accompanied by hypoproteinemia also causes a decrease in the serum globulins. This is known as hypoglobulinemia. Of the different types of globulins, gamma globulin is believed to be the one concerned with the formation of antibodies. Some have referred to it as the antibody globulin. To the best of our knowledge no chemical methods have as yet been discovered for its quantitative estimation.

Gamma globulin therefore plays an important role in imparting to the system resistance to infections. Studies have been conducted to determine the nature of its amino-acid composition. The following have been isolated and identified: arginine, histidine, lysine, cysteine, methionine, tryptophane, threonine, tyrosine, serine, hydroxyproline, and leucine. There are at least five indispensable amino acids among the constituents of gamma globulin. These essential amino acids have to be derived from the protein intake as they cannot be synthesized by the body except at the expense of sacrificing other tissue proteins. On the other hand, the synthesis of cysteine and cystine depends upon methionine. If methionine is lacking or is not present in sufficient amounts, cysteine and cystine have to be incorporated in the diet. The synthesis of tyrosine depends on phenylalanine and unless phenylalanine is supplied in sufficient amounts to furnish the body with its own phenylalanine and with an abundant supply for the synthesis of tyrosine, the latter also has to be present in the diet.

Globulin synthesis in the body therefore depends upon amino-acid production. An abundance of gamma globulin in serum protein is necessary to increase resistance to infections.

3. *Edema.* A study of the history of epidemics reveals that under conditions of war, of imprisonment and of famine, nutritional edema has been found to be frequent and associated with beriberi. It has also been noted that this type of edema disappears when the undernourished inflicted with this disorder are given adequate food intake, rich in protein and vitamins.

Rats kept on a low protein intake diet but given adequate amounts of other foodstuffs and accessory factors developed edema. This observation was made some

twenty-seven years ago and since has been repeatedly confirmed. Some of the animals that were used for this study developed lung infections and died. Invariably low serum protein level was noted. In this connection, it has been observed by some investigators that the fluid intake is of importance. They pointed out that if the fluid intake is reduced no edema develops even though the serum proteins are actually low.

Experimental work on dogs that were kept on a low protein intake show that when edema develops, serum protein level is about 4 grams per 100 cc. On fractionating the serum protein it was found to contain only 2 grams of albumin. In man 5 grams of serum protein is indicative of hypoproteinemia, since the normal is between 7 and 8 grams per 100 cc.

4. *Nutritional Anemia.* Herein we are not concerned with a discussion of anemia, its etiology and treatment. However, we must recognize the intimate relationship that exists between protein and iron deficiencies. It is obvious that the main constituents of hemoglobin are proteins and iron. Thus an inadequate intake of protein for a sufficiently long period of time is bound to influence not only plasma protein formation but also hemoglobin regeneration.

According to Castle, nutritional anemias may be divided into two groups: (1) the direct or primary types, which are caused by inadequate diet, and (2) the conditional or secondary types, resulting from inadequate utilization by the body of an otherwise complete diet.

A decrease of gastric secretions, the development of achlorhydria, edema of the gastrointestinal tract, and other such disorders are frequent occurrences in subjects suffering from protein deficiency. These disorders doubtless interfere with the proper absorption of iron. Thus in this sense a vicious circle develops, and it becomes imperative to correct the primary factors causing nutritional anemia by giving adequate amounts of protein in the diet, as well as non-irritating iron salts, preferably ferrous compounds that are soluble at about neutrality.

In a recent study on 50 unselected cases of anemia among a population of adult male Indians (17,000 meat eaters and 1,188 vegetarians), the incidence, types and severity of anemia was found to depend on the meat content of the diet. Nutritional macrocytic anemia occurred only in vegetarians in this series of cases. Earlier, macrocytic anemia was reported in 56 patients whose diets had been inadequate in animal protein and in the vitamins of the B complex.

The hemoglobin-forming properties of the various individual amino acids has also been studied in rats and it has been found that a combination of amino acids in as yet undetermined proportions is necessary for the synthesis of the protein molecule. Studying anemic dogs, Whipple and co-workers are of the opinion that histidine and phenylalanine in both their natural and synthetic forms exert a definite influence on the regeneration of hemoglobin.

Recent clinical findings indicate that hypoproteinemia and anemia commonly occur in patients with

gastrointestinal diseases. For example, in a series of 97 cases of gastric carcinoma, 59 per cent of the patients had hypoproteinemia and 70 per cent hypochromic anemia.

By and large there seems to be overwhelming evidence pointing to the importance of adequate protein intake as well as iron for the correction of nutritional anemia.

PROTEIN DEFICIENCY IN PREGNANCY AND LACTATION

For many years the protein requirement of women in pregnancy and lactation has been the subject of considerable interest to investigators in this field. Their findings indicate that the pregnant woman should receive 1.5 grams of protein per kilogram of body weight and the lactating woman, 2.0 grams of protein per kilogram of body weight. The 1942 recommendation of the Committee on Food and Nutrition of the National Research Council was 85 grams and 100 grams of protein for the average pregnant and lactating woman, respectively.

Recently several clinicians surveyed the food intake of various groups in widely separated areas and their findings showed that the average daily intake of protein during pregnancy was about 66 grams. Such low protein intake is indeed critical and leads to marked disorders. Prolonged protein deficiency in the pregnant woman not only impairs her health and brings about serious complications but endangers the general health of her offspring. It often results in serious injuries that are at times difficult to correct in the short period prior to delivery.

During the early stages of protein deficiency the pregnant woman is in negative nitrogen balance. Unless this condition is recognized and corrected by adequate protein feeding to bring about not only nitrogen equilibrium but positive nitrogen balance, loss of appetite, loss of weight, dizziness and marked fatigue are bound to become evident.

Some of the disorders resulting from protein deficiency during pregnancy are well recognized.

Hypoproteinemia and Edema. Loss of serum protein arises from the depletion of tissue proteins. This decrease in the serum protein level, particularly the albumin fraction, alters the colloidal osmotic pressure of the blood and is probably the major causative factor of nutritional edema and one of the causes of the toxemias of pregnancy.

Anemia. Anemias of pregnancy are very well known and have also been attributed to protein deficiency. It is believed that the prevailing hypoproteinemia, by bringing about an alteration in the permeability of the gastrointestinal tract, impairs the absorption of iron, of calcium, and of vitamins. It is doubtful that the administration of iron and calcium medications and of vitamins, without increasing the protein intake, can correct such disturbances. Hypoproteinemia must be corrected by the administration of whole blood, plasma, or amino acids or by increasing the protein intake.

Decreased Resistance to Infections. Since invariably on a protein-deficient diet the plasma protein level is reduced, both albumin and globulin fractions are also affected, particularly gamma globulin. The latter was shown to play an important role in imparting resistance to infections. In correcting protein deficiency it is advisable that the protein intake be gradually raised until the desired amount is reached. In addition, the carbohydrate intake must be adequate so that the absorbed protein will be spared for the wear and tear of the body and for the building of new tissues. In pregnancy there is a great demand by the fetus on the protein reserve of the mother. This demand has to be met and can be supplied only by increasing the protein in the diet. During lactation the continued demands on plasma protein for the synthesis of milk are well recognized. The growth of the breast alone requires a storage of 17 grams of nitrogen. The human infant in its early weeks consumes from 1 to 1½ grams of nitrogen daily. This is a great drainage on the mother and her protein intake has to be raised by 2 grams for every gram of nitrogen in the milk. Thus the high allowance of protein during lactation has been recommended as was pointed out earlier in this discussion.

EXCESSIVE EXCRETION OF NITROGEN, AS IN BURNS, SURGERY, ETC.

Moderate to severe injury invariably causes excessive nitrogen deficit. This nitrogen deficit may be caused by (1) loss of actual tissues as in severe burns, (2) loss of blood or exudates from the injured areas as in severe wounds and bleeding ulcers, (3) increased catabolism following injury, (4) poor absorption caused by nausea, trauma, shock, vomiting, diarrhea, etc., and (5) tissue degeneration caused by disuse and reflex atrophy.

Excessive nitrogen output has been observed in cases of severe burns, and amounts of 25 grams up to 45 grams of daily urinary nitrogen have been reported. Such losses are indeed staggering and become more impressive when interpreted in terms of protein or tissue loss. For example, a loss of 45 grams of urinary nitrogen per day represents a loss of about 280 grams of protein or approximately 1750 grams of tissue on the assumption that the protein content of tissue is about 16 per cent. In a recent issue of the *Lancet*, it was reported that the protein losses of a 60 per cent burn case involving the whole thickness of the skin amounted to (1) about 700 grams in the mass of skin and other underlying tissues destroyed, (2) 600 grams in the exudates, (3) 700-800 grams caused by catabolic processes, and (4) about 100 grams from atrophy due to disuse. In other words, there was a total protein loss of about 2200 grams and, in terms of tissue loss, 13,750 grams or approximately 30 pounds.

Excessive nitrogen loss has also been reported in cases of fractures and dislocations, and tissue losses have been estimated at about 8 per cent of the total body protein for the first 10 days after injury.

Protein deficiency brought about by moderate to

severe injury occurs so rapidly that hypoproteinemia, edema, impaired functions of the gastrointestinal tract, anemia, liver damage, and decreased resistance to infections develop at a much faster rate than in malnutrition. Most observers in this field are of the opinion that the maintenance of nitrogen balance during the first ten days after the injury is beyond control despite the administration of large amounts of proteins, amino-acid mixture or enzymatic digests of certain proteins. It is assumed that the nitrogen derived from the tissues destroyed and the prevailing metabolic disturbances resulting in increased catabolic processes need to be eliminated. The nitrogen intake, whether administered parenterally or orally, cannot be fully utilized under the circumstances to counter balance the nitrogen output. However, a high protein diet along with sufficient caloric intake and the necessary accessory factors and essential minerals must be given to suppress, at the earliest opportunity, the existing nitrogen deficit. Recently Croft and Peters demonstrated in burned rats that by doubling the protein intake and including one per cent *dl*-methionine, nitrogen equilibrium was attained.

The findings of Croft and Peters are indeed significant, but they have not as yet been confirmed in man. However, they should stimulate clinical investigations on the quantitative indispensable amino-acid requirements for man in health and in disease. Obviously, if the protein of the injured tissue has among its constituents a higher content of at least one of its indispensable amino acids than is found in the amino-acid mixture given, then the amount of the latter to be given has to be doubled. To clarify this statement, let us assume that for the synthesis of a certain protein the cell requires a mixture of amino acids as found among the cleavage products of casein. In such a case one molecule of casein would be sufficient to furnish the cell with its amino-acid requirement to permit the synthesis of one molecule of its protein. However, if the pattern of protein of this particular cell calls for a 7 per cent methionine, and casein can furnish only 3.5 per cent of this amino acid, then to synthesize one molecule of its protein would require either two molecules of casein or one molecule of casein plus the additional amount of methionine.

Another factor that should be considered is the species requirement. The rat requirement of essential amino acids differs qualitatively and quantitatively from other species and particularly from that of man. In the burned rat there is damage to both skin and fur. The protein of the latter is well known to be rich in sulfur amino acids. As to the skin, its characteristic protein is an albuminoid, which is also characterized by its high sulfur content of which most is in the form of cystine. It has already been pointed out that for the synthesis of cystine adequate intake of methionine must be given. Casein or casein hydrolysate is relatively poor in this amino acid. It has approximately 3.5 per cent methionine and a maximum of 0.4 per cent cystine, whereas the albuminoid of skin has about 15 per cent cystine.

Protein deficiency has been observed to be prevalent among patients with gastrointestinal diseases, decubitous ulcers, ulcers of various other types, hyperthyroidism, cancer, hepatic diseases, and recent observers in this field are of the opinion that general surgical cases are prone to be protein deficient. The causes of protein deficiency in the surgical patient are also numerous. There may be impaired digestion, due to dysfunction of the secretions of the gastrointestinal tract, poor absorption due to edema of the gastrointestinal wall, obstructions, liver damage, renal damage, increased catabolic processes due to glandular disorders or infections, hemorrhage, diarrhea, etc. In their recent review, Lund and Levenson stated, "The estimation of the status of a surgical patient with regard to the presence or degree of protein deficiency is not simple. The factors necessary for a critical evaluation are: (1) optimum weight of patient, (2) observed weight of patient, (3) plasma protein level, (4) plasma albumin level, (5) plasma volume, and (6) nitrogen intake and nitrogen output. In surgical patients, particularly, one is frequently confronted by situations in which an acute disturbance has occurred in a patient with chronic protein deficiency. When this happens, the acute changes may intensify or mask the chronic ones, depending on the direction of change."

It is therefore important that whenever possible protein deficiency be corrected during the preoperative stage. Preferably this should be done by oral feeding of a high protein, high caloric and high vitamin diet. The food should be palatable and appealing, and every effort should be made to induce the patient to consume it. Should hypoproteinemia be in an advanced stage and should the diet act as an irritant, causing diarrhea, then parenteral feeding should be advocated. In general, it may be said that during illness there is lack of appetite. The parenteral administration of plasma followed by amino acids with adequate carbohydrates and vitamins should be attempted. The correction of hypoproteinemia renders the patient a better surgical risk.

During the operative stage the surgeon is quite often concerned with the condition of his patient during anesthesia. Most anesthetics have a more or less definite effect on glycogen distribution and hyperglycemia. Several investigators have demonstrated that ether anesthesia markedly lowers the glycogen content of the heart of cats. Others have shown in the same species that it lowers muscle glycogen and causes a considerable mobilization of liver glycogen with a rise in blood sugar. Barbiturates also have a marked influence on carbohydrate metabolism. Recently Casten reported that hypoproteinemia develops during anesthesia. Whether this is due to a shift in the dynamic equilibrium between plasma and reserve protein or to an impairment of the functions of the liver is not known. There is reason to believe that deep anesthesia does interfere with liver functions.

Hyperglycemia following deep anesthesia is probably caused by the stimulation of the adrenal gland and the mobilization of epinephrine. Physiological

doses of epinephrine cause rapid mobilization of glucose from liver glycogen.

Some eighteen years ago the author investigated the effect of deep anesthesia on blood sugar in surgery in the experimental animal. He noted marked elevation of blood sugar accompanied by glycosuria. The administration of small doses of insulin caused a suppression of glycosuria and a lowering of blood sugar. There was also a marked improvement in appetite. The anesthetized operated animals that were not treated with insulin remained nauseated and in a stage of stupor for a longer time. They also refrained from eating their food.

The parenteral administration of glucose or glucose and amino acids immediately following anesthesia and surgery is now a common practice. However, a considerable amount of sugar is probably excreted in the urine. This can be controlled by the administration of about 5 to 10 units of insulin.

Amino acids are glucogenic but the blood sugar mobilization occurs at a slow rate and over a period of several hours. The curve shown in Fig. 1 represents

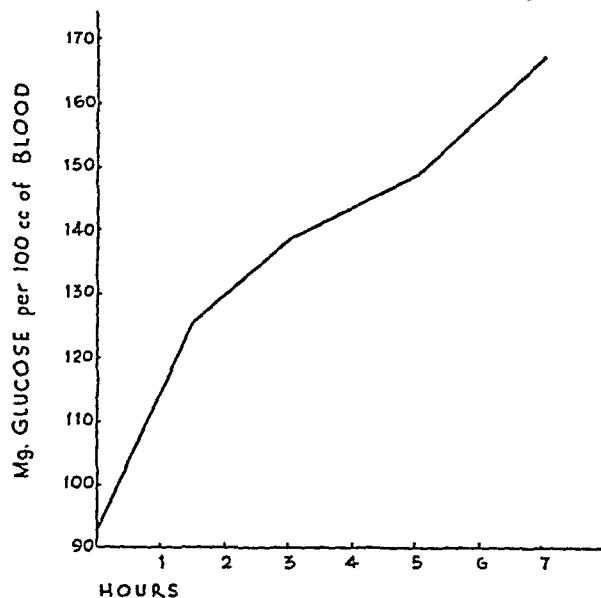


Fig. 1—Blood sugar formation following the subcutaneous injection of 1 gram per kilogram of a complete amino-acid mixture into rabbits. The curve represents the averages of the blood sugars of 10 animals.

the averages of blood sugars of 10 rabbits that were given 1 gram of a complete amino-acid mixture (Paranamine) per kilogram of body weight. Unfortunately, this experiment was not carried out for a sufficient length of time to determine the optimum rise and the return of blood sugar to normal levels. These results indicate that it would be advisable to control carbohydrate metabolism after the administration of glucose or glucose and amino acids into surgical patients following anesthesia. A considerable rise in blood sugar may be encountered under the circumstances, which does not enhance the feeling of well-being. In fact, it may lead to the formation of acidosis and may explain the development of nausea and vomiting which has been observed by clinicians.

Recently several investigators have noted a rise in

blood sugar in burn cases, and the degree of hyperglycemia was considered by some to be in direct ratio to the extent of the burn. This hyperglycemia was of several hours duration and in some instances of several days. In certain burn cases, high blood sugar was

accompanied by initial decrease in carbon dioxide combining power and lactic acidemia. These observations obviously indicate an acute disturbance in carbohydrate metabolism and strongly suggest the judicious use of compensatory amounts of insulin under such conditions.

REFERENCES

1. Abbott, W. E. and Mellors, R. C.: Body Fluid Studies in Experimental Obstruction at Various Levels of the Gastrointestinal Tract. *Surgery*, 12:445, 1942.
2. Abbott, W. E., Mellors, R. C. and Muntwyler, E.: Fluid, Protein and Electrolyte Alterations in Experimental Intestinal Obstruction. *Ann. Surg.*, 117:39, 1943.
3. Abbott, W. E. and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients with Dehydration and Malnutrition. Indications for Intravenous Alimentation with Amino Acids. *Arch. Surg.*, 46:277, 1943.
4. Abels, J. C., Rekers, P. E., Martin, H. E. and Rhoads, C. P.: The Relationship between Dietary Deficiency and Occurrence of Papillary Atrophy of the Tongue and Oral Leukoplakia. *Cancer Research*, 2:381, 1942.
5. Adair, F. L.: Influence of Diet on Lactation. *Am. J. Obst. & Gynec.*, 9:1, 1925.
6. Adair, G. S. and Robinson, M. E.: Analysis of Osmotic Pressures of Serum Proteins, and Molecular Weights of Albumins and Globulins. *Biochem. J.*, 24:993, 1930.
7. Adamson, J. D., Joliffe, N., Kruse, H. D., Lowry, O. H., Moore, P. E., Platt, B. S., Sebrell, W. H., Tice, J. W., Tisdall, F. F., Wilder, R. M. and Zamecnik, P. C.: Medical Survey of Nutrition in Newfoundland. *Canadian M. A. J.*, 52:227, 1945.
8. Addis, T.: Proteinuria and Cylindruria. *Proc. California Acad. Med.*, p. 38, 1931-32.
9. Addis, T., Poo, L. J. and Lew, W.: The Quantities of Protein Lost by the Various Organs and Tissues of the Body During a Fast. *J. Biol. Chem.*, 115:111, 1936.
10. Addis, T., Poo, L. J. and Lew, W.: Protein Loss from the Liver During a Two Day Fast. *J. Biol. Chem.*, 115:117, 1936.
11. Addis, T., Poo, L. J. and Lew, W.: The Rate of Protein Formation in Organs and Tissues of the Body After Casein Re-feeding. *J. Biol. Chem.*, 116:343, 1936.
12. Addis, T.: Metabolism of Intraperitoneally Injected Serum Protein. *Proc. Soc. Exper. Biol. & Med.*, 40:336, 1939.
13. Aguilar, H. D.: Tratamiento de las quemaduras graves, con especial consideración de la hipoproteïnemia. *Prensa méd. argent.*, 31:1446, 1944. *Abstr.: Int. Surg. Dig.*, 38:372, 1944.
14. Albanese, A. A., Holt, L. E., Jr., Brumback, J. E., Jr., Hayes, M., Kajdi, C. and Wangerin, D. M.: Nitrogen Balance in Experimental Lysine Deficiency in Man. *Proc. Soc. Exper. Biol. & Med.*, 48:728, 1941.
15. Albanese, A. A. and Buschke, W.: On Cataract and Certain Other Manifestations of Tryptophane Deficiency in Rats. *Science*, 95:584, 1942.
16. Albanese, A. A., Holt, L. E., Jr., Kajdi, C. N. and Frankston, J. E.: Observations on Tryptophane Deficiency in Rats—Chemical and Morphological Changes in the Blood. *J. Biol. Chem.*, 148:299, 1943.
17. Albanese, A. A., Holt, L. E., Jr., Brumback, J. E., Jr., Kajdi, C. N., Frankston, J. E. and Wangerin, D. M.: Nitrogen Balance in Experimental Human Deficiencies of Methionine and Cystine. *Proc. Soc. Exper. Biol. & Med.*, 52:18, 1943.
18. Albanese, A. A., Randall, R. M. and Holt, L. E., Jr.: Effect of Tryptophane Deficiency on Reproduction. *Science*, 97:312, 1943.
19. Albanese, A. A. and Irby, V.: Observations on Biological Value of a Mixture of Essential Amino Acids. *Science*, 98:286, 1943.
20. Albanese, A. A., Holt, L. E., Jr., Frankston, J. E. and Irby, V.: Observations on Histidine Deficient Diet in Man. *Bull. Johns Hopkins Hosp.*, 74:251, 1944.
21. Albanese, A. A., Holt, L. E., Jr., Brumback, J. E., Jr., Frankston, J. E. and Irby, V.: Observations on a Diet Deficient in Both Methionine and Cystine in Man. *Bull. Johns Hopkins Hosp.*, 74:308, 1944.
22. Albanese, A. A.: The Utilization of α -Amino Acids by Man: I. Tryptophane, Methionine and Phenylalanine. *Bull. Johns Hopkins Hosp.*, 75:175, 1944.
23. Albanese, A. A.: The Utilization of α -Amino Acids by Man. II. Cystine. *J. Biol. Chem.*, 158:101, 1945.
24. Albright, F. and Browne, J. S. L.: Josiah Macey, Jr. Foundation Report of Conference on Bone and Wound Healing. Second Meeting, December 11-12, 1942, p. 55.
25. Alcock, R. S.: Role of Tryptophane in Blood Development. *Biochem. J.*, 27:754, 1933.
26. Allison, J. B. and Anderson, J. A.: The Relation Between Absorbed Nitrogen, Nitrogen Balance and Biological Value of Proteins in Adult Dogs. *J. Nutrition*, 29:413, 1945.
27. Altschuler, S. S., Hensel, H. M. and Sahyun, M.: Maintenance of Nitrogen Equilibrium of Amino Acids Administered Parenterally. *Am. J. M. Sc.*, 200:239, 1940.
28. Altschuler, S. S., Hensel, H. M., Hecht, P. and Pursley, R.: Maintenance of Nitrogen Equilibrium by Intravenous Administration of Amino Acids. *Arch. Int. Med.*, 70:749, 1942.
29. Altschuler, S. S., Sahyun, M., Schneider, H. and Satriano, D.: Clinical Use of Amino Acids for the Maintenance of Nitrogen Equilibrium. *J. A. M. A.*, 121:163, 1943.
30. Anderson, T. F. and Roberts, J. L.: Macrocytic Anaemias in Kenya—Preliminary Report. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 33:615, 1940.
31. Appleton, V. B.: Observation on Deficiency Disease in Laboratory. *Am. J. Pub. Health*, 11:617, 1921.
32. Ariel, I., Rekers, P. E., Pack, G. T. and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: X. Hypoproteinemia and Anemia in Patients with Gastric Cancer. *Ann. Surg.*, 118:366, 1943.
33. Ariel, I., Abels, J. C., Pack, G. T. and Rhoads, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: XI. Postoperative Hypoproteinemia and Relationship of Serum Protein Fall to Urinary Nitrogen Excretion. *Surg., Gynec. & Obst.*, 77:16, 1943.
34. Armstrong, S. H., Jr., England, A. C., Favour, C. B. and Scheinberg, I. H.: Anemia and Hypoproteinemia Complicating Severe Protracted Pneumonia: Treatment with Penicillin: Role of Specific Supportive Therapy in Recovery. *J. A. M. A.*, 127:303, 1945.
35. Arnell, R. E. and Guerriero, W. F.: Nutritional Edema in Pregnancy with Analysis of Eight Severe Cases. *Am. J. Obst. & Gynec.*, 43:467, 1942.
36. Arnell, R. E., Guerriero, W. F., Goldman, D. W., Huckleby, E. and Lutz, A. M.: Protein Malnutrition in Pregnancy. *New Orleans M. & S. J.*, 95:114, 1942.
37. Arnell, R. E., Goldman, D. W. and Bertucci, F. J.: Protein Deficiencies in Pregnancy. *J. A. M. A.*, 127:1101, 1945.
38. Ashburn, P. M.: Epidemic of Albuminuria. *J. A. M. A.*, 90:535, 1928.
39. Ashford, B. K.: Sprue. *Ann. Clin. Med.*, 4:13, 1925.
40. Barden, R. P., Ravdin, I. S. and Frazier, W. D.: Hypoproteinemia as a Factor in the Retardation of Gastric Emptying After Operations of Billroth I or II Types. *Am. J. Roentgenol.*, 38:196, 1937.
41. Barden, R. P., Thompson, W. D., Ravdin, I. S. and Frank, L. L.: The Influence of the Serum Protein on the Motility of the Small Intestine. *Surg., Gynec. & Obst.*, 66:819, 1938.
42. Barnett, C. W., Jones, R. B. and Cohn, R. B.: Maintenance of Normal Plasma Protein Concentration in Spite of Repeated Protein Loss by Bleeding. *J. Exper. Med.*, 55:683, 1932.
43. Bartels, E. C.: Serum Protein Studies in Hyperthyroidism. *New England J. Med.*, 218:289, 1938.
44. Bass, M. H.: Deficiency Anemia in Infants. Report of Two Cases, with Associated Temporary Deficiency of Antianemic Factor in One and Allergy and Abnormal Digestion of Protein in the Other. *Am. J. Dis. Child.*, 67:341, 1944.
45. Bassett, S. H., Woods, R. R., Shull, F. W. and Madden, S. C.: Parenterally Administered Amino Acids as a Source of Protein in Man. *New England J. Med.*, 230:106, 1944.
46. Beach, E. F., Munks, B., Robinson, A. and Macy, I. G.: Dietary Evaluation of Animal Proteins from Their Amino Acid Contents. *J. Am. Dietet. A.*, 19:570, 1943.
47. Beiling, C. A. and Lee, R. E.: Treatment of Hypoproteinemia by Oral Administration of Protein Hydrolysate. *Arch. Surg.*, 43:735, 1941.

48. Berg, C. P. and Potgieter, M.: Tryptophane Metabolism: II. The Growth Promoting Ability of *dl*-Tryptophane. *J. Biol. Chem.*, 94:661, 1932.
49. Berg, C. P.: The Availability of *d*(-)-Lysine for Growth. *J. Nutrition*, 12:671, 1936.
50. Berglund, H. and Frick, A. R.: Further Observations on the Mode of Protein Elimination, Particularly of Induced Variations and Proteinuria. *Acta med. Scandinav.*, 96:255, 1938.
51. Berry, L. J., Davis, J. and Spies, T. D.: The Relationship Between Diet and the Mechanisms for Defense Against Bacterial Infections in Rats. *J. Lab. & Clin. Med.*, 50:684, 1945.
52. Berryman, G. H., Bollman, J. L. and Mann, F. C.: Influence of Liver on Proteins of Blood Plasma. *Am. J. Physiol.*, 139:556, 1943.
53. Bethell, F. H.: The Blood Changes in Normal Pregnancy and Their Relation to the Iron and Protein Supplied by the Diet. *J. A. M. A.*, 107:564, 1936.
54. Bethell, F. H., Gardiner, S. H. and MacKinnon, F.: The Influence of Iron and Diet on the Blood in Pregnancy. *Ann. Int. Med.*, 13:91, 1939.
55. Binger, M. W. and Keith, N. M.: General Edema of Indeterminate Etiology. *J. A. M. A.*, 109:1, 1937.
56. Binkley, G. E., Abels, J. C. and Rhoads, C. P.: The Treatment of Postoperative Hypoproteinemia in Patients with Cancer of the Colon and Rectum. *Ann. Surg.*, 117:748, 1943.
57. Blackman, S. S., Jr., Goodwin, W. E. and Buell, M. V.: On the Relation Between the Concentration of Total Protein and of Globulin in Urine and Pathogenesis of Certain Renal Lesions in Bright's Disease. *Bull. Johns Hopkins Hosp.*, 69:397, 1941.
58. Block, R. J. and Bolling, D.: Nutritional Opportunities with Amino Acids. *J. Am. Dietet. A.*, 20:69, 1944.
59. Block, R. J. and Bolling, D.: The Amino Acid Composition of Proteins and Foods. Springfield, Illinois: C. C. Thomas, 1945.
60. Bloomfield, A. L.: Effect of Restriction of Protein Intake on Serum Protein Concentration of Rat. *J. Exper. Med.*, 57:705, 1933.
61. Bloomfield, A. L.: The Effect of Various Protein Rations on the Serum Protein Concentration of the Rat. *J. Exper. Med.*, 61:465, 1935.
62. Boyd, J. D.: Prescribed Diets for Normal Children. *J. Pediat.*, 24:616, 1944.
63. Brown, R. B. and McCray, P. M.: Serum Proteins Before and After Operations for Hyperthyroidism. *Endocrinology*, 22:502, 1938.
64. Browne, J. S. L.: Josiah Macey, Jr. Foundation Report of Conference on Bone and Wound Healing. Second Meeting, December 11-12, 1942, p. 50.
65. Browne, J. S. L., Schenker, V. and Stevenson, J. A. F.: Some Metabolic Aspects of Damage and Convalescence. *J. Clin. Investigation*, 23:932, 1944.
66. Bruckman, F. S. and Peters, J. P.: The Plasma in Relation to Blood Hydration: V. Serum Protein and Malnutritional and Cachetic Edema. *J. Clin. Investigation*, 8:591, 1930.
67. Brunschwig, A., Clark, D. E. and Corbin, N.: Symposium on Abdominal Surgery: Postoperative Nitrogen Losses and Studies on Parenteral Nitrogen Nutrition by Means of Casein Digest. *Ann. Surg.*, 115:1091, 1942.
68. Burden, N. J.: Albuminuria. Its Clinical Significance When Occurring in Otherwise Healthy Young Men. *Pennsylvania M. J.*, 37:32, 1933.
69. Burden, N. J.: Persistent Functional Albuminuria. *Am. J. M. Sc.*, 188:242, 1934.
70. Burke, B. S.: Need for Better Nutrition During Pregnancy and Lactation. *J. Am. Dietet. A.*, 17:102, 1941; *M. Women's J.*, 48:81, 1941.
71. Burke, B. S., Beal, V. A., Kirkwood, S. B. and Stuart, H. C.: Nutrition Studies During Pregnancy. *Am. J. Obst. & Gynec.*, 46:38, 1943.
72. Burke, B. S., Harding, V. V. and Stuart, H. C.: Nutrition Studies During Pregnancy. IV. Relation of Protein Content of Mother's Diet During Pregnancy to Birth Length, Birth Weight, and Condition of Infant at Birth. *J. Pediat.*, 23:506, 1943.
73. Butler, A. M.: Nutritional Requirements in Infancy and in Childhood. *Am. J. Dis. Child.*, 64:898, 1942.
74. Butt, H. R., Snell, A. M. and Keys, A.: Plasma Protein in Hepatic Disease. *Arch. Int. Med.*, 63:143, 1939.
75. Calvin, D. B.: Plasma Volume and Plasma Protein Concentration After Severe Hemorrhage. *J. Lab. & Clin. Med.*, 26:1144, 1941.
76. Cannon, P. R.: Antibodies and the Protein-Reserves. *J. Immunol.*, 44:107, 1942.
77. Cannon, P. R., Chase, W. E. and Wissler, R. W.: The Relationship of the Protein-Reserves to Antibody Production: The Effects of a Low-Protein Diet and of Plasmapheresis on the Formation of Agglutinins. *J. Immunol.*, 47:133, 1943.
78. Cannon, P. R., Wissler, R. W., Woolridge, R. L. and Benditt, E. P.: The Relationship of Protein Deficiency to Surgical Infection. *Ann. Surg.*, 120:514, 1944.
79. Cannon, P. R.: Protein Metabolism and Acquired Immunity. *J. Am. Dietet. A.*, 20:77, 1944.
80. Cannon, P. R.: Protein Metabolism and Resistance to Infection. *J. Michigan M. Soc.*, 43:323, 1944.
81. Cannon, P. R.: The Importance of Proteins in Resistance to Infection. *J. A. M. A.*, 128:360, 1945.
82. Cartwright, G. E., Wintrobe, M. M., Buschke, W. H., Follis, R. H., Jr., Suksta, A. and Humphreys, S.: Anemia, Hypoproteinemia, and Cataracts in Swine Fed Casein Hydrolysate or Zein. Comparison with Pyridoxine-Deficiency Anemia. *J. Clin. Investigation*, 24:268, 1945.
83. Casten, D. and Bodenheimer, M.: The Problem of Hypoproteinemia in Surgical Patients. *Surg., Gynec. & Obst.*, 72:178, 1941.
84. Casten, D., Bodenheimer, M. and Barcham, I.: A Study of Plasma Protein Variations in Surgical Patients. *Ann. Surg.*, 117:52, 1943.
85. Cerecedo, L. R. and Foy, J. R.: Relationship Between Protein Intake and Pyridoxine Deficiency in the Rat. The Role of Tryptophane and Cystine. *Fed. Proc.*, 3:55, 1944.
86. Chang, H. C.: Plasma Protein and Blood Volume. *Proc. Soc. Exper. Biol. & Med.*, 29:829, 1932.
87. Channen, H. J. and Wilkinson, H.: Protein and the Dietary Production of Fatty Livers. *Biochem. J.*, 29:350, 1935.
88. Chase, B. W. and Lewis, H. B.: The Rate of Absorption of Leucine, Valine and Their Isomers from the Gastrointestinal Tract of the White Rat. *J. Biol. Chem.*, 106:315, 1934.
89. Church, C. F.: Factors Influencing Non-Specific Resistance to Infection. *Am. J. Pub. Health*, 29:215, 1939.
90. Clark, A. H.: The Effect of Diet on the Healing of Wounds. *Bull. Johns Hopkins Hosp.*, 30:117, 1919.
91. Clark, D. E., Brunschwig, A. and Corbin, N.: Utilization of Parenterally Administered Casein Digest for Synthesis of Proteins. *Proc. Soc. Exper. Biol. & Med.*, 49:282, 1942.
92. Clark, D. E. and Brunschwig, A.: Intravenous Nourishment with Protein, Carbohydrate and Fat in Man. *Proc. Soc. Exper. Biol. & Med.*, 49:329, 1942.
93. Clavelin, C. and Hugonot: Oedème généralisé chez un brûlé. Contribution à la pathogénie des oedèmes. *Bull. et mém. Soc. méd. d. hôp. de Paris*, 52:1444, 1936.
94. Clayton, M. M.: Protein in the Low Cost Diet. *J. Am. Dietet. A.*, 18:462, 1942.
95. Cohn, E. J., Oncley, J. L., Strong, L. F., Hughes, W. L., Jr. and Armstrong, S. H., Jr.: The Characterization of the Protein Fractions of Human Plasma. *J. Clin. Investigation*, 23:417, 1944.
96. Conn, J. W.: The Advantage of a High Protein Diet in the Treatment of Spontaneous Hypoglycemia. *J. Clin. Investigation*, 15:673, 1936.
97. Connell, H. C.: Importance of Protein Intake in Cancer. *Canad. M. A. J.*, 52:64, 1945.
98. Cook, M. M.: Diarrheal Diseases in the Newborn Infant. *J. Missouri M. A.*, 40:64, 1943.
99. Cooke, J. V.: Proteose Intoxications and Injury of the Body Protein. *J. Exper. Med.*, 28:223, 1918.
100. Coons, C. M., Schiefelbusch, A. T., Marshall, G. B. and Coons, R. R.: Studies in Metabolism During Pregnancy. Bulletin 223, Oklahoma Agricultural Experiment Station, 1935.
101. Cope, O., Nathanson, I. T., Rourke, G. M. and Wilson, H.: Metabolic Observations. (Management of the Coconut Grove Burns at the Massachusetts General Hospital). *Ann. Surg.*, 117:937, 1943.
102. Co Tui, Wright, A. M., Mulholland, J. H., Barcham, I. and Brex, E. S.: The Nutritional Care of Cases of Extensive Burns, with Special Reference to the Oral Use of Amino-Acids (Amigen) in Three Cases. *Ann. Surg.*, 119:815, 1944.
103. Co Tui, Wright, A. M., Mulholland, J. H., Carabba, V., Barcham, I. and Vinci, V. J.: Studies on Surgical Convalescence. I. Sources of Nitrogen Loss Postgastrectomy and Effect of High Amino-Acid and High Caloric Intake on Convalescence. *Ann. Surg.*, 120:99, 1944.
104. Cox, W. M., Jr. and Mueller, A. J.: Serum Albumin Regeneration as Affected by Intravenously and Orally Administered Protein Hydrolysates. *J. Clin. Investigation*, 23:875, 1944.
105. Cox, W. M., Jr. and Mueller, A. J.: Relative Efficiency of Three Forms of Intravenously Administered Nitrogen on Nitrogen Balance and Amino Acid Excretion. *Am. J. Dis. Child.*, 69:328, 1945.

106. Crandall, L. A., Jr.: The Clinical Significance of the Plasma Proteins. *Memphis M. J.*, 19:146, 1944.
107. Croft, P. B. and Peters, R. A.: Nitrogen Loss After Thermal Burns. Effects of Adding Protein and Methionine to Diet of Rats. *Lancet*, 1:266, 1945.
108. Croft, P. B. and Peters, R. A.: Effect of Methionine upon Nitrogen Losses in the Urine Following Severe Burns. *Nature*, London, 155:175, 1945.
109. Curtis, P. B., Hauge, S. M. and Kraybill, H. R.: The Nutritive Value of Certain Animal Protein Concentrates. *J. Nutrition*, 5:503, 1932.
110. Cuthbertson, D. P.: Further Observations on the Disturbance of Metabolism Caused by Injury, with Particular Reference to the Dietary Requirements of Fracture Cases. *Brit. J. Surg.*, 23:505, 1936.
111. Cuthbertson, D. P.: Post-Shock Metabolic Response (Arris and Gale Lecture). *Lancet*, 1:433, 1942.
112. Cuthbertson, D. P.: Protein Metabolism. *Brit. Med. Bull.*, 2:207, 1944.
113. Cuthbertson, D. P.: Dietary Protein in Relation to Convalescence from Injury. *Nutrition Society. Lancet*, 1:786, 1945.
114. Daft, F. S., Robschheit-Robbins, F. S. and Whipple, G. H.: New Formed Hemoglobin and Protein Catabolism. Conservation of Intermediates in the Anemic Dog on a Protein-Free Diet. *J. Biol. Chem.*, 103:495, 1933.
115. Daft, F. S., Robschheit-Robbins, F. S. and Whipple, G. H.: Abscess Nitrogen Metabolism in Anemic and Non-Anemic Dog. Reserve Stores of Protein Apparently Involved. *J. Biol. Chem.*, 121:45, 1937.
116. Daft, F. S., Robschheit-Robbins, F. S. and Whipple, G. H.: Plasma Protein Given by Vein and Its Influence upon Body Metabolism. *J. Biol. Chem.*, 123:87, 1938.
117. Daniels, A. L., Hutton, M. K., Knott, E. M., Wright, O. E., Everson, G. J. and Schouler, F.: A Study of the Protein Needs of Preschool Children. *J. Nutrition*, 9:91, 1935.
118. Darmady, E. M.: The Effects of Protein Diet on Infective Hepatitis. *Brit. M. J.*, June 9, 1945, p. 795.
119. Davis, H. H.: Amino Acids Intravenously in Surgical Patients. *Nebraska M. J.*, 30:51, 1945.
120. Davis, H. H.: The Routine Use of Protein Digest Intravenously Following Major Surgical Procedures. *Surg., Gynec. & Obst.*, 81:31, 1945.
121. Day, C. D. M.: Nutritional Deficiencies and Dental Caries in Northern India. *Brit. Dent. J.*, 76:115, 143, 1944.
122. Deaver, J. W., Cronkite, E. P. and Phillips, R. B.: Severe Burn. Case Report. Notes on Abnormal Nitrogen Metabolism. *U. S. Nav. M. Bull.*, 42:1162, 1944.
123. Derow, H. A. and Stellar, L. I.: Evaluation of Albuminuria. *J. A. M. A.*, 123:503, 1943.
124. Dieckmann, W. J. and Kramer, S.: Proteinuria in Toxemia of Pregnancy. *J. A. M. A.*, 120:590, 1942.
125. Diehl, H. S. and McKinley, C. A.: Albuminuria in College Men. *Arch. Int. Med.*, 49:45, 1932.
126. Eastman, N. J.: Serum Proteins in Toxemias of Pregnancy. *Am. J. Obst. & Gynec.*, 19:343, 1930.
127. Ebbs, J. H., Tisdall, F. F. and Scott, W. A.: The Influence of Prenatal Diet on the Mother and Child. *J. Nutrition*, 22:515, 1941.
128. Ebert, R. V., Stead, E. A., Jr., Warren, J. V. and Watts, W. E.: Plasma Protein Replacement After Hemorrhage in Dogs With and Without Shock. *Am. J. Physiol.*, 136:299, 1942.
129. Elders, C.: Tropical Sprue and Pernicious Anaemia, Aetiology and Treatment. *Lancet*, 1:75, 1925.
130. Elman, R. and Weiner, D. O.: Intravenous Alimentation. *J. A. M. A.*, 112:796, 1939.
131. Elman, R.: Time Factor in Retention of Nitrogen After Intravenous Injection of a Mixture of Amino Acids. *Proc. Soc. Exper. Biol. & Med.*, 40:484, 1939.
132. Elman, R.: Certain Surgical Aspects of Protein Metabolism. *Tr. Kansas City Acad. Med.*, p. 51, 1939-41.
133. Elman, R.: Acute Hypoproteinemia Following a Single Severe Hemorrhage in the Fasting Dog. *Am. J. Physiol.*, 128:332, 1940.
134. Elman, R.: Symposium on Fluid and Electrolyte Needs of Surgical Patients: Parenteral Replacement of Protein with Amino Acids of Hydrolyzed Casein. *Ann. Surg.*, 112:594, 1940.
135. Elman, R.: Serum Albumin Regeneration Following Intravenous Amino Acids (Hydrolyzed Casein) in Hypoproteinemia Produced by Severe Hemorrhage. *Proc. Soc. Exper. Biol. & Med.*, 43:14, 1940.
136. Elman, R.: Therapeutic Significance of Plasma Protein Replacement in Severe Burns. *J. A. M. A.*, 116:213, 1941.
137. Elman, R. and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on Morphology, Function, and Protein and Water Content of Liver. *J. Exper. Med.*, 73:417, 1941.
138. Elman, R.: Correction of Protein Deficiencies in Surgical Patients. *Washington Univ. M. Alumni Quart.*, 4:81, 1941.
139. Elman, R., Weiner, D. O. and Bradley, E.: Intravenous Injections of Amino-Acids (Hydrolyzed Casein) in Postoperative Patients. *Ann. Surg.*, 115:1160, 1942.
140. Elman, R., Sachar, L. A., Horvitz, A. and Wolf, H.: Regeneration of Serum Albumin with Hydrolyzed Protein in Chronic Hypoproteinemia Produced by Diet. *Experimental Study. Arch. Surg.*, 44:1064, 1942.
141. Elman, R.: Recent Advances in Surgery, Particularly from the Standpoint of Improving Prognosis, with Special Reference to the Correction of Protein Deficiencies. *Connecticut M. J.*, 6:913, 1942.
142. Elman, R.: Protein Deficiency in Surgical Patients and Its Correction. *J. Am. Dietet. A.*, 18:141, 1942.
143. Elman, R.: Acute Protein Deficiency (Hypoproteinemia) in Surgical Shock Due to Severe Hemorrhage and in Biliary Intestinal Obstruction and General Peritonitis, with Special Reference to the Use of Plasma and Hydrolyzed Protein. *J. A. M. A.*, 120:1176, 1942.
144. Elman, R., Brown, F. A., Jr. and Wolf, H.: Studies on Hypoalbuminemia Produced by Protein-Deficient Diets. Rapid Correction of Hypoalbuminemia with Ad Libitum Meat Diet. *J. Exper. Med.*, 75:461, 1942.
145. Elman, R.: The Oral Use of Amino-Acids of Hydrolyzed Casein (Amigen) in Surgical Patients. *Am. J. Digest. Dis.*, 10:48, 1943.
146. Elman, R., Lischer, C. E. and Davey, H. W.: Plasma Proteins (Albumins and Globulins) and Red Cell Volume Following Single Severe Non-Fatal Hemorrhage. *Am. J. Physiol.*, 138:569, 1943.
147. Elman, R. and Lischer, C. E.: Amino-Acids, Serum and Plasma in the Replacement Therapy of Fatal Shock Due to Repeated Hemorrhage. An Experimental Study. *Ann. Surg.*, 118:225, 1943.
148. Elman, R., Davey, H. W. and Loo, Y.: Influence of Histidine on Urinary Excretion of Nitrogen in Dogs Given Pure Amino Acid Mixtures Intravenously. *Arch. Biochem.*, 3:45, 1943.
149. Elman, R., Charnas, R. and Davey, H. W.: Ceiling of Utilization of Nitrogen. Effect of Continuous Venoclysis with Amino Acids of Hydrolyzed Protein During Experimental Hypoalbuminemia. *Arch. Surg.*, 47:216, 1943.
150. Elman, R., Smith, M. R. and Sachar, L. A.: Correlation of Cytological with Chemical Changes in Liver as Influenced by Diet, Particularly Protein. *Gastroenterology*, 1:24, 1943.
151. Elman, R. and Lischer, C. E.: Treatment of Experimental Shock from Repeated Hemorrhage. Preliminary Report on the Use of Pure Amino Acids and of Hydrolyzed Protein. *J. A. M. A.*, 121:498, 1943.
152. Elman, R. and Davey, H. W.: Studies on Hypoalbuminemia Produced by Protein-Deficient Diets: Correction of Hypoalbuminemia in Dogs by Means of Large Plasma Transfusions. *J. Exper. Med.*, 77:1, 1943.
153. Elman, R.: Symposium on Nutrition. Protein Metabolism and Practice of Medicine. *M. Clin. North America*, 27:303, 1943.
154. Elman, R. and Lischer, C.: Occurrence and Correction of Hypoproteinemia (Hypoalbuminemia) in Surgical Patients. *Collective Review. Surg., Gynec. & Obst.*, 76:503, 1943.
155. Elman, R.: Acute Starvation Following Operation or Injury: With Special Reference to Caloric and Protein Needs. *Ann. Surg.*, 120:350, 1944.
156. Elman, R.: Parenteral Fluids and Food in Gastrointestinal Disease. *Bull. New York Acad. Med.*, 20:220, 1944.
157. Elman, R.: Maintenance of Nitrogen Balance by the Intravenous Administration of Plasma Proteins and Protein Hydrolysates. *Physiol. Rev.*, 24:372, 1944.
158. Elman, R.: The Practical Use of Amino Acids in Protein Nutrition. *J. A. M. A.*, 128:659, 1945.
159. Eufinger, H.: Die Kolloidstruktur des plasmas während der gravidität. *Klin. Wchnschr.*, 7:492, 1928.
160. Evans, J. A. and Boehme, E. J.: Amino Acid Therapy in Hypoproteinemic Surgical Patient. *S. Clin. North America*, 23:887, 1943.
161. Evers, F. C.: Significance of Albuminuria. *Proc. A. Life Insur. M. Dir. America*, 22:8, 1935.
162. Fagin, I. D. and Zinn, F. T.: Cirrhosis of the Liver. Results of Treatment with Parenterally Administered Amino Acids. *J. Lab. & Clin. Med.*, 27:1400, 1942.
163. Fagin, I. D., Sahyun, M. and Pagel, R. W.: Cirrhosis of the Liver: The Lipotropic Action of Parenterally Administered

- Amino Acids. *J. Lab. & Clin. Med.*, 28:987, 1943.
164. Fairley, N. H., Bromfield, R. J., Foy, H. and Kondi, A.: Nutritional Macrocytic Anemia in Macedonia. *Tr. Roy. Soc. Trop. Med. & Hyg.*, 32:132, 1938.
165. Farr, L. E. and Van Slyke, D. D.: The Relation Between Plasma Protein Level and Edema in Nephrotic Children. *Am. J. Dis. Child.*, 57:306, 1939.
166. Farr, L. E.: Intravenous Administration of Small Doses of Casein Hydrolysate to Nephrotic Children and Its Effect Upon Nitrogen Balance and Plasma Amino Acid Level. *J. Pediat.*, 16:679, 1940.
167. Farr, L. E., Emerson, K., Jr. and Fletcher, P. H.: Comparative Nutritive Efficiency of Intravenous Amino Acids and Dietary Protein in Children with Nephrotic Syndrome. *J. Pediat.*, 17:595, 1940.
168. Farr, L. E.: Indications for the Therapeutic Use of Intravenous Amino Acids. *Connecticut M. J.*, 5:24, 1941.
169. Feller, A. E. and Fowler, W. M.: Hyperproteinemia in Multiple Myeloma. *J. Lab. & Clin. Med.*, 23:369, 1938.
170. Fine, J. and Seligman, A. M.: Traumatic Shock. Study of the Problem of "Lost Plasma" in Hemorrhagic Shock by the Use of Radioactive Plasma Protein. *J. Clin. Investigation*, 22:285, 1943.
171. Fine, J. and Seligman, A. M.: Traumatic Shock. Study of the Problem of "Lost Plasma" in Hemorrhagic, Tourniquet, and Burn Shock by the Use of Radioactive Iodo-plasma Protein. *J. Clin. Investigation*, 23:720, 1944.
172. Fink, R. M., Enns, T., Kimball, C. P., Silberstein, H. E., Bale, W. F., Madden, S. C. and Whipple, G. H.: Plasma Protein Metabolism — Normal and Associated with Shock. Observations Using Protein Labelled by Heavy Nitrogen in Lysine. *J. Exper. Med.*, 80:455, 1944.
173. Foord, A. G.: Hyperproteinemia, Autohemagglutination, Renal Insufficiency and Abnormal Bleeding in Multiple Myeloma. *Ann. Int. Med.*, 8:1071, 1935.
174. Gardner, C. E., Jr. and Trent, J. C.: Intravenous Amino Acid Administration in Surgical Patients Using an Enzymatic Casein Digest. *Surg., Gynec. & Obst.*, 75:657, 1942.
175. Garry, R. C. and Stiven, D.: Review of Recent Work on Dietary Requirements in Pregnancy and Lactation, with an Attempt to Assess Human Requirements. *Nutrition Abst. & Rev.*, 5:855, 1936.
176. Gaunt, W. E.: Protein Hydrolysates in Intravenous Alimention. *Nutrition Abst. & Rev.*, 13:501, 1944.
177. Gordon, H. H., Levine, S. Z., Wheatley, M. A. and Marples, E.: Respiratory Metabolism in Infancy and in Childhood. XX. The Nitrogen Metabolism in Premature Infants — Comparative Studies of Human Milk and Cow's Milk. *Am. J. Dis. Child.*, 54:1030, 1937.
178. Graham, C. and Poulton, E. P.: The Influence of High Temperature on Protein Metabolism with Reference to Fever. *Quart. J. Med.*, 6:82, 1912.
179. Gray, S. J. and Barron, E. S. G.: Electrophoretic Analyses of Serum Proteins in Diseases of the Liver. *J. Clin. Investigation*, 22:191, 1943.
180. Groen, J. and Snapper, I.: Dietary Deficiency as a Cause of Macrocytic Anemia. *Am. J. M., Sc.*, 193:633, 1937.
181. Grossman, M. I. and Ivy, A. C.: Diet and Cancer. *Gastroenterology*, 4:186, 1945.
182. Guerrant, R. E. and Hogan, A. G.: Effect of Amino Acids on Anemia Caused by Deaminized Casein. *J. Biol. Chem.*, 128:363, 1939.
183. Gutman, A. B. and Gutman, E. B.: Relation of Serum Calcium to Serum Albumin and Globulins. *J. Clin. Investigation*, 16:903, 1937.
184. Gutman, A. B., Moore, D. H., Gutman, E. B., McClellan, V. and Kabat, E. A.: Fractionation of Serum Proteins in Hyperproteinemia, with Special Reference to Multiple Myeloma. *J. Clin. Investigation*, 20:765, 1941.
185. Hahn, P. F. and Whipple, G. H.: Hemoglobin Production in Anemia Limited by Low Protein Intake. Influence of Iron Intake, Protein Supplements and Fasting. *J. Exper. Med.*, 69:315, 1939.
186. Hamilton, T. S.: Growth Activity and Composition of Rats Fed Diets Balanced and Unbalanced with Respect to Protein. *J. Nutrition*, 17:565, 1939.
187. Hanson, S.: Constancy of Protein Quotient. *J. Immunology*, 3:67, 1918.
188. Harden, B., McElroy, W. S. and Huggins, R. R.: Protein Stabilization in Preeclampsia and Eclampsia. *Am. J. Obst. & Gynec.*, 30:524, 1935.
189. Harkins, H. N.: The Treatment of Burns. Springfield, Illinois: Charles C. Thomas, 1942.
190. Harkins, H. N., Cope, O., Evans, E. I., Phillips, R. A. and Richards, D. W., Jr.: The Fluid and Nutritional Therapy of Burns. *J. A. M. A.*, 128:475, 1945.
191. Harkins, H. N.: The Present Status of the Problem of Thermal Burns. *Physiol. Rev.*, 25:531, 1945.
192. Harrell, G. T. and Fisher, S.: Blood Chemical Change in Boeck's Sarcoid with Particular Reference to Protein, Calcium, and Phosphatase Values. *J. Clin. Investigation*, 18:687, 1939.
193. Harris, H. A., Neuberger, A. and Sanger, F.: Lysine Deficiency in Young Rats. *Biochem. J.*, 37:508, 1943.
194. Hartmann, A. F., Meeker, C. S., Perley, A. M. and McGinnis, H. G.: Studies of Amino Acid Administration. Utilization of Enzymatic Digest of Casein. *J. Pediat.*, 20:308, 1942.
195. Hartmann, A. F., Lawler, H. J. and Meeker, C. S.: Studies of Amino Acid Administration. II. Clinical Uses of an Enzymatic Digest of Casein. *J. Pediat.*, 24:371, 1944.
196. Hartmann, A. F.: Parenteral Administration of Amino Acids. *J. Pediat.*, 26:193, 1945.
197. Hartzell, J. B., Winfield, J. M. and Irvin, J. L.: Plasma, Vitamin C and Serum Protein Levels in Wound Disruption. *J. A. M. A.*, 116:669, 1941.
198. Harvey, S. C. and Howes, E. L.: Effect of High Protein Diet on the Velocity of Growth of Fibroblasts in the Healing Wound. *Ann. Surg.*, 91:641, 1930.
199. Hawks, J. E., Bray, M. M. and Dye, M.: The Influence of Diet on the Nitrogen Balances of Preschool Children. *J. Nutrition*, 15:125, 1938.
200. Heidelberger, M., Treffers, H. P., Schoenheimer, R., Ratner, S. and Rittenberg, D.: Behavior of Antibody Protein Toward Dietary Nitrogen in Active and Passive Immunity. *J. Biol. Chem.*, 144:555, 1942.
201. Higgins, G., O'Brien, J. R. P., Peters, R. A., Stewart, A. and Witts, L. J.: Treatment of Infective Hepatitis with Methionine. *Brit. M. J.*, 1:401, 1945.
202. Hill, L. W.: Amino Acids as a Source of Nitrogen for Allergic Infants. *J. A. M. A.*, 116:2135, 1941.
203. Hirshfeld, J. W., Williams, H. H., Abbott, W. E., Heller, C. G. and Pilling, M. A.: Significance of the Nitrogen Loss in the Exudate from Surface Burns. *Surgery*, 15:766, 1944.
204. Hirshfeld, J. W., Abbott, W. E., Pilling, M. A., Heller, C. G., Meyer, F., Williams, H. H., Richards, A. J. and Obi, R.: Metabolic Alterations Following Thermal Burns. III. Effect of Variations in Food Intake on Nitrogen Balance of Burned Patients. *Arch. Surg.*, 50:194, 1945.
205. Hoelzel, F. and DaCosta, E.: Production of Ulcers in Protonach of Rats by Protein Restriction. *Proc. Soc. Exper. Biol. & Med.*, 29:382, 1932.
206. Holman, R. L., Mahoney, E. B. and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet. I. Liver and Casein as Potent Diet Factors. *J. Exper. Med.*, 59:251, 1934.
207. Holman, R. L., Mahoney, E. B. and Whipple, G. H.: Blood Plasma Protein Given by Vein Utilized in Body Metabolism. II. A Dynamic Equilibrium Between Plasma and Tissue Proteins. *J. Exper. Med.*, 59:269, 1934.
208. Holmes, O. M.: Protein Diet in Pregnancy. *West. J. Surg.*, 49:56, 1941.
209. Holt, L. E. and Fales, H. L.: The Food Requirement of Children: II. Protein Requirement. *Am. J. Dis. Child.*, 22:371, 1921.
210. Holt, L. E., Jr., Albanese, A. A., Brumback, J. E., Jr., Kajdi, C. and Wangerin, D. M.: Nitrogen Balance in Experimental Tryptophane Deficiency in Man. *Proc. Soc. Exper. Biol. & Med.*, 48:726, 1941.
211. Holt, L. E., Jr., Albanese, A. A., Shettles, L. B., Kajdi, C. and Wangerin, D. M.: Studies of Experimental Amino Acid Deficiency in Man. I. Nitrogen Balance. *Fed. Proc.*, 1: (Pt. 2) 116, 1942.
212. Holt, L. E., Jr., Albanese, A. A., Frankston, J. E. and Irby, V.: The Tryptophane Requirement of Man as Determined by Nitrogen Balance and by Excretion of Tryptophane in Urine. *Bull. Johns Hopkins Hosp.*, 75:353, 1944.
213. Howard, J. E.: Studies on Protein Metabolism in Fractures. *Bull. Johns Hopkins Hosp.*, 74:313, 1944.
214. Howard, J. E., Winternitz, J., Parson, W., Bigham, R. S., Jr. and Eisenberg, H.: Studies on Fracture Convalescence. Influence of Diet on Post-Traumatic Nitrogen Deficit Exhibited by Fracture Patients. *Bull. Johns Hopkins Hosp.*, 75:209, 1944.
215. Howes, E. L. and McKeown, R. M.: Influence of a Diet Rich in Casein on the Strength of Bone and the Healing of Fractures. *Arch. Surg.*, 29:786, 1934.
216. Howland, J. W. and Hawkins, W. B.: Protein Metabolism, Protein Interchange, and Utilization in Phlorh'zinized Dogs. *J. Biol. Chem.*, 123:99, 1938.
217. Janeway, C. A.: The Plasma Proteins: Their Importance in

- Clinical Medicine and Surgery. New England J. Med., 229: 751, 779, 1943.
218. Janeway, C. A.: Clinical Use of Products of Human Plasma Fractionation: I. Albumin in Shock and Hypoproteinemia. J. A. M. A., 126:674, 1944.
 219. Jeghers, H. and Selesnick, S.: Hyperproteinemia: Its Significance. Internat. Clin., 3:248, 1937.
 220. Jeghers, H.: Nutrition. New England J. Med., 225:687, 1941.
 221. Jeghers, H.: Nutrition: The Appearance of the Tongue as an Index of Nutritional Deficiency. New England J. Med., 227:221, 1942.
 222. Johansen, A. H.: Hypoproteinemia. Acta Path. et Microb. Scandinav., Suppl. 37:272, 1938.
 223. Johnson, D.: High-Protein Diets. J. Am. Dietet. A., 20:666, 1944.
 224. Jones, C. M. and Eaton, F. B.: Postoperative Nutritional Edema. Arch. Surg., 27:159, 1933.
 225. Jones, C. M., Eaton, F. B. and White, J. C.: Experimental Postoperative Edema. Arch. Int. Med., 53:649, 1934.
 226. Jones, C. M.: Protein Deficiency. New England J. Med., 215:1152, 1936.
 227. Kagan, B. M.: Studies on Clinical Significance of Serum Proteins. Protein Content of Normal Human Venous and Capillary Serum and Factors Affecting Accuracy of Its Determination. J. Lab. & Clin. Med., 27:1457, 1942.
 228. Kagan, B. M.: Hyperglobulinemia. Am. J. M. Sc., 206:309, 1943.
 229. Kagan, B. M.: Studies on Clinical Significance of Serum Proteins. Relationship Between Albumin-Globulin Ratio, Albumin, Globulin and Total Protein. Arch. Int. Med., 71:157, 1943.
 230. Kagan, B. M.: Clinical Significance of Serum Proteins. South. M. J., 36:234, 1943.
 231. Kern, R. A.: Diet as a Factor in the Etiology of Anemia. Ann. Int. Med., 5:729, 1931.
 232. Kerr, W. J.: Regeneration of Blood Proteins. Am. J. Physiol., 47:356, 370, 379, 1918.
 233. Kessler, W. F.: Observations on the Use of Amino Acids in the Treatment of Certain Diseases. Med. Times, 73:131, 1945.
 234. Kik, M. C.: Nutritive Value of Lactalbumin Versus Casein. Proc. Soc. Exper. Biol. & Med., 37:129, 1937.
 235. Kinsey, V. E. and Grant, W. M.: Adequacy of Essential Amino Acids for Growth of Rat. Science, 99:303, 1944.
 236. Kleczkowski, A.: Formation of Protein Complexes in Heated Solutions of Rabbit Serum Proteins. Brit. J. Exper. Path., 22:188, 1941.
 237. Kleczkowski, A.: Effect of Salts on Formation of Protein Complexes During Heat Denaturation. Biochem. J., 37:30, 1943.
 238. Knutti, R. E., Erickson, C. C., Madden, S. C., Rekers, P. E. and Whipple, G. H.: Liver Function and Blood Plasma Protein Formation. J. Exper. Med., 65:455, 1937.
 239. Koehne, M. and Morrell, E.: Food Requirement of Girls from 6 to 13 Years of Age. Am. J. Dis. Child., 47:548, 1934.
 240. Kooser, J. H.: Observations on Possible Relationship of Diet to Late Toxemia of Pregnancy. Am. J. Obst. & Gynec., 41:288, 1941.
 241. Koster, H. and Shapiro, A.: Serum Proteins and Wound Healing. Arch. Surg., 41:723, 1940.
 242. Koster, H. and Kasman, L. P.: Relation of Serum Protein to Well Healed and to Disrupted Wounds. Arch. Surg., 45:776, 1942.
 243. Kozoll, D. D., Hoffman, W. S. and Meyer, K. A.: Nitrogen Balance Studies on Surgical Patients Receiving Amino Acids. Observations on Patients with Obstructing Lesions of the Esophagus and Stomach Receiving Amino Acids by Parenteral Injections as the Exclusive Source of Protein. Arch. Surg., 51:59, 1945.
 244. Krejci, L. E., Jennings, R. K. and Smith, L. D.: Influence of Non-Specific Protein on Heat Inactivation of Antibody to Pneumococcal Polysaccharide. Electrophoretic Investigation of Heat Inactivation of Antibody in Presence of Casein. J. Immunol., 45:111, 1942.
 245. Krieger, V. J. and Rome, R. M.: Toxaemia Pregnancy in Relation to Subsequent Pregnancies, with Special Reference to Renal Function Tests. M. J. Australia, 1:597, 1941.
 246. Krishnan, K. V., Narayanan, E. K. and Sankaran, G.: Protein Hydrolyzates in Treatment of Inanition. Indian M. Gaz., 79: 160, 1944.
 247. Kyer, J. and Bethell, F. H.: Production of Macrocytic Anemia in the Pregnant Rat by Diets Low in Protein. Arch. Path., 25:767, 1938.
 248. Lauener, P.: Benign Albuminuria in Children. Schweiz. med. Wchnschr., 52:1170, 1922.
 249. Leamy, C. M.: State Nutrition Program from Nutritionist's Point of View. Child, 6:37, 1941.
 250. Lee, R. I.: Albuminuria in Young Men. M. Clinics N. America, 3:1059, 1920.
 251. Lepore, M. J.: Experimental Edema Produced by Plasma Protein Depletion. Proc. Soc. Exper. Biol. & Med., 23:311, 1931.
 252. Lepore, M. J.: Experimental Edema Produced by Plasma Protein Depletion. Arch. Int. Med., 50:488, 1932.
 253. Lepore, M. J.: Relation of Plasma Volume to Plasma Protein Concentration. Proc. Soc. Exper. Biol. & Med., 30:268, 1932.
 254. Levine, S. Z.: Protein Nutrition in Pediatrics. J. A. M. A., 128:283, 1945.
 255. Levy, J. S. and Siler, K. A.: Clinical Studies of Amino Acid Effects of Oral Administration of Solution of Amino Acid Mixture on Gastric Acidity. Am. J. Digest. Dis., 9:354, 1942.
 256. Levy, J. S.: The Effect of Oral Administration of "Amino Acids" on the Hypoproteinemia Resulting from Bleeding Peptic Ulcer. Gastroenterology, 4:375, 1945.
 257. Lewis, H. B.: Handbook of Nutrition. Proteins in Nutrition. J. A. M. A., 120:198, 1942.
 258. Lippard, V. W., Schloss, O. M. and Johnson, P. A.: Immune Reactions Induced in Infants by Intestinal Absorption of Incompletely Digested Cow's Milk Protein. Am. J. Dis. Child., 51:562, 1936.
 259. Lischer, C. E., Elman, R. and Davey, H. W.: Influence of Alimentation on Regeneration of Plasma Proteins Following Single Severe Non-Fatal Hemorrhage. Am. J. Physiol., 139: 638, 1943.
 260. Liu, S. H., Chu, H. I., Wang, S. H. and Chung, H. L.: Nutritional Edema. Effects of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema. Chinese J. Physiol., 6:73, 1932.
 261. Liu, S. H., Chu, H. I., Li, R. C. and Fan, C.: Nutritional Edema. Effect of Alkali and Acids on Nitrogen Balance, Plasma Proteins, and Edema. Chinese J. Physiol., 6:95, 1932.
 262. Lucido, J.: Metabolic and Blood Chemical Changes in Severe Burns: Case Report. Ann. Surg., 111:640, 1940.
 263. Luck, J. M.: Liver Proteins. Question of Protein Storage. J. Biol. Chem., 115:491, 1936.
 264. Luetscher, J. A., Jr.: Effect of Single Injection of Concentrated Human Serum Albumin on Circulating Proteins and Proteinuria in Nephrosis. J. Clin. Investigation, 23:365, 1944.
 265. Lund, C. C. and Levenson, S. M.: Protein in Surgery. J.A.M.A. 128:95, 1945.
 266. Lusk, G.: The Science of Nutrition. Philadelphia: W. B. Saunders Company, 1928, pp. 75-117.
 267. Lyall, A.: Classification of Cases of Albuminuria. Brit. M. J., 2:113, 1941.
 268. Macy, I. G.: Nutrition and Chemical Growth in Childhood. Vol. I. Evaluation. Springfield, Illinois: Charles C. Thomas, 1942, p. 402.
 269. Madden, S. C., Winslow, P. M., Howland, J. W. and Whipple, G. H.: Blood Plasma Protein Regeneration as Influenced by Infection, Digestive Disturbances, Thyroid, and Food Protein: Deficiency State Related to Protein Depletion. J. Exper. Med., 65:431, 1937.
 270. Madden, S. C., George, W. E., Waraich, G. S. and Whipple, G. H.: Blood Plasma Protein Regeneration as Influenced by Fasting, Infection, and Diet Factors. Variable Reserve Stores of Plasma Protein Building Material in Dog. J. Exper. Med., 67:675, 1938.
 271. Madden, S. C., Noehren, W. A., Waraich, G. S. and Whipple, G. H.: Blood Plasma Protein Production as Influenced by Amino Acids. Cystine Emerges as Key Amino Acid Under Fixed Conditions. J. Exper. Med., 69:721, 1939.
 272. Madden, S. C., Finch, C. A., Swalbach, W. G. and Whipple, G. H.: Blood Plasma Protein Production and Utilization. Influence of Amino Acids and of Sterile Abscesses. J. Exper. Med., 71:283, 1940.
 273. Madden, S. C. and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization. Physiol. Rev., 20:194, 1940.
 274. Madden, S. C., Turner, A. P., Rowe, A. P. and Whipple, G. H.: Blood Plasma Protein Production as Influenced by Various Degrees of Hypoproteinemia and by Amino Acids. J. Exper. Med., 73:571, 1941.
 275. Madden, S. C., Zeldis, L. J., Hengerer, A. D., Miller, L. I., Rowe, A. P., Turner, A. P. and Whipple, G. H.: Casein Digests Parenterally Utilized to Form Blood Plasma Protein. J. Exper. Med., 73:727, 1941.
 276. Madden, S. C., Carter, J. R., Kattus, A. A., Jr., Miller, L. I. and Whipple, G. H.: Ten Amino Acids Essential for Plasma Protein Production Effective Orally or Intravenously. J. Exper. Med., 77:277, 1943.
 277. Madden, S. C., Woods, R. R., Shull, F. W. and Whipple, G. H.: Blood Plasma Protein Production as Influenced by Amino Acids. J. Exper. Med., 73:571, 1941.

- G. H.: Amino Acid Mixtures Effective Parenterally for Long Continued Plasma Protein Production. Casein Digests Compared. *J. Exper. Med.*, 79:607, 1944.
278. Madden, S. C., Woods, R. R., Shull, F. W., Remington, J. H. and Whipple, G. H.: Tolerance to Amino Acid Mixtures and Casein Digests Given Intravenously: Glutamic Acid Responsible for Reactions. *J. Exper. Med.*, 81:439, 1945.
279. Madden, S. C. and Clay, W. A.: Protein Metabolism and Protein Reserves During Acute Sterile Inflammation. High Protein Intake Compensates for Increased Catabolism. *J. Exper. Med.*, 82:65, 1945.
- 279a. Magee, H. E.: Physiological Basis of Starvation Symptoms. *Brit. M. J.*, 1:818, June 9, 1945.
280. Mann, H. C. C.: Diets for Boys During School Age. Medical Research Council, Special Report Series, No. 105, London, His Majesty's Stationery Office, 1926.
281. Maroney, J. W. and Johnston, J. A.: Caloric and Protein Requirements and Basal Metabolism of Children from 4 to 14 Years. *Am. J. Dis. Child.*, 54:29, 1937.
282. Martin, G. J. and Thompson, M. R.: Intravenous Alimentionation with Amino Acids. Review. *Medicine*, 22:73, 1943.
283. Martin, G. J.: Mixtures of Pure Amino Acids as Substitutes for Dietary Protein. *Proc. Soc. Exper. Biol. & Med.*, 55:182, 1944.
284. Matzner, M. J., Windwer, C. and Sobel, A. E.: The Role of Protein in the Prevention of Experimental Gastric Ulcers. *Am. J. Digest. Dis.*, 5:36, 1938.
285. McCance, R. A., Widdowson, E. M. and Verdon-Roe, C. M.: Study of English Diets by Individual Method. Pregnant Women at Different Economic Levels. *J. Hyg.*, 38:596, 1938.
286. McCance, R. A., Widdowson, E. M. and Lehmann, H.: Effect of Protein Intake on Absorption of Calcium and Magnesium. *Biochem. J.*, 36:686, 1942.
287. McCollum, E. V. and Davis, M.: The Influence of the Plane of Protein Intake on Growth. *J. Biol. Chem.*, 20:415, 1915.
288. McCollum, E. V., Orent-Keiles, E. and Day, H. G.: The Newer Knowledge of Nutrition. New York: Macmillan Company, 1939. Chapter 4, page 120.
289. McGinty, D. A., Lewis, H. B. and Marvel, C. S.: Amino Acid Synthesis in the Animal Organism. *J. Biol. Chem.*, 62:75, 1924.
290. McMichael, J.: Clinical Aspects of Shock. *J.A.M.A.*, 124:275, 1944.
291. McNaught, J. B., Scott, V. C., Woods, F. M. and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet. Effects of Plant Proteins Compared with Animal Proteins. The Influence of Fasting and Infection. *J. Exper. Med.*, 63:277, 1936.
292. Mearay, P. M., Jr., Barden, R. P. and Ravdin, I. S.: Nutritional Edema: Its Effect on the Gastric Emptying Time Before and After Gastric Operations. *Surgery*, 1:53, 1937.
293. Mellanby, E.: Nutrition and Disease. The Interaction of Clinical and Experimental Work. London: Oliver and Boyd, 1934.
294. Melnick, D., Cowgill, G. R. and Burack, E.: Influence of Diet Upon Regeneration of Serum Proteins. Standardization of Experimental Technique. *J. Exper. Med.*, 64:877, 1936.
295. Melnick, D., Cowgill, G. R. and Burack, E.: The Influence of Diet Upon the Regeneration of Serum Protein. II. The Potency Ratios of Serum Protein, Lactalbumin and Casein, and the Effect of Tissue-Protein Catabolism on the Formation of Serum Protein. *J. Exper. Med.*, 64:897, 1936.
296. Melnick, D. and Cowgill, G. R.: The Serum Protein Complex as a Factor in Regulating Blood Volume. *Proc. Soc. Exper. Biol. & Med.*, 35:312, 1936.
297. Melnick, D. and Cowgill, G. R.: Influence of Prolonged, Intensive Plasmapheresis Upon the Ability of an Organism to Regenerate Serum Protein. *J. Exper. Med.*, 66:493, 1937.
298. Melnick, D. and Cowgill, G. R.: Influence of Pregnancy and Lactation Upon Regeneration of Serum Protein. *J. Exper. Med.*, 66:509, 1937.
299. Melnick, D. and Cowgill, G. R.: The Protein Minima for Nitrogen Equilibrium with Different Proteins. *J. Nutrition*, 13:401, 1937.
300. Melnick, D. and Cowgill, G. R.: Problem of Hypoproteinemia. *Yale J. Biol. & Med.*, 10:49, 1937.
301. Melnick, D.: Protein in Human Nutrition. With Particular Reference to the Role of the Essential Amino Acids. Wallerstein Laboratories Communications, 6:167, 1943.
302. Messinger, W. J. and Hawkins, W. B.: Arspenamine Liver Injury Modified by Diet: Protein and Carbohydrate Protective, but Fat Injurious. *Am. J. M. Sc.*, 199:216, 1940.
303. Metcalf, W.: Fate and Effects of Transfused Serum or Plasma in Normal Dogs. *J. Clin. Investigation*, 23:403, 1944.
304. Metcalf, J., Favour, C. B. and Stare, F. J.: Plasma Protein and Hemoglobin in the Protein Deficient Rat: A Three Dimensional Study. *J. Clin. Investigation*, 24:82, 1945.
305. Metcalf, J., Goldsmith, G. A., McQueeney, A. J., Dove, R. F., McDevitt, E., Dove, M. A. and Stare, F. J.: Nutritional Survey in Norris Point, Newfoundland. *J. Lab. & Clin. Med.*, 30:475, 1945.
306. Meyer, K. A. and Kozoll, D. D.: Protein Deficiency in Surgical Patients. *Surg., Gynec. & Obst.*, 78:181, 1944.
307. Miller, L. L. and Whipple, G. H.: Chloroform Liver Injury Increases as Protein Stores Decrease: Studies in Nitrogen Metabolism in These Dogs. *Am. J. M. Sc.*, 199:204, 1940.
308. Miller, L. L., Ross, J. F. and Whipple, G. H.: Methionine and Cystine. Specific Protein Factors Preventing Chloroform Liver Injury in Protein Depleted Dogs. *Am. J. M. Sc.*, 200:739, 1940.
309. Miller, L. L., Robscheit-Robbins, F. S. and Whipple, G. H.: Hemoglobin and Plasma Protein: Their Relation to Internal Body Protein Metabolism. *J. Exper. Med.*, 81:405, 1945.
310. Mills, C. A. and Cottingham, E.: Phagocytic Activity as Affected by Protein Intake in Heat and Cold. *J. Immunol.*, 47:503, 1943.
311. Minot, G. R.: Nutritional Deficiency. *Ann. Int. Med.*, 12:429, 1938.
312. Mitchell, H. H.: A Method of Determining the Biological Value of Protein. *J. Biol. Chem.*, 58:873, 903, 1923.
313. Mitchell, H. H.: The Nutritive Value of Proteins. *Physiol. Rev.*, 4:424, 1924.
314. Mitchell, H. H.: Determination of the Nutritive Value of the Proteins of Food Products. *Ind. Eng. Chem., An. Ed.*, 16:696, 1944.
315. Mitchell, H. S.: A Nutrition Survey in Labrador and Northern Newfoundland. *J. Am. Dietet. A.*, 6:29, 1930.
316. Moise, T. S. and Smith, A. H.: Diet and Tissue Growth. I. The Regeneration of Liver Tissue on Various Adequate Diets. *J. Exper. Med.*, 40:13, 1924.
317. Moore, C. V., Vilter, R., Minnich, V. and Spies, T. D.: Nutritional Macrocytic Anemia in Patients with Pellagra or Deficiency of the Vitamin B Complex. *J. Lab. & Clin. Med.*, 29:1226, 1944.
318. Moore, N. S. and Van Slyke, D. D.: Relationships Between Plasma Specific Gravity, Plasma Protein Content, and Edema in Nephritis. *J. Clin. Investigation*, 8:337, 1930.
319. Moss, A. R.: The Conversion of Beta-Phenylacetic Acid to Tyrosine in Normal Rats. *J. Biol. Chem.*, 137:739, 1941.
320. Mueller, A. J., Kemmerer, K. S., Cox, W. M., Jr. and Barnes, S. T.: The Effect of Casein and a Casein Digest on Growth and Serum Protein Regeneration. *J. Biol. Chem.*, 134:573, 1940.
321. Mueller, A. J., Fickas, D. and Cox, W. M., Jr.: Minimum Maintenance Requirement of Enzymic Casein Hydrolysate. *Bull. Johns Hopkins Hosp.*, 72:110, 1943.
322. Mulholland, J. H., Co Tui, Wright, A. M. and Vinci, V. J.: Nitrogen Metabolism, Caloric Intake and Weight Loss in Post-operative Convalescence. Study of 8 Patients Undergoing Partial Gastrectomy for Duodenal Ulcers. *Ann. Surg.*, 117:512, 1943.
323. Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V. and Shafiroff, B.: Protein Metabolism and Bed Sores. *Ann. Surg.*, 118:1015, 1943.
324. Munks, Bertha. Supplying Adequate Amino Acid Intakes with Food. *Med. Woman's J.*, 52:21, 1945.
325. Munro, H. N. and Cuthbertson, D. P.: The Response of Protein Metabolism to Injury. *Biochem. J.*, 37:xii, 1943.
326. Muntwyler, E., Way, C. T., Binns, D. and Myers, V. C.: Plasma Protein and Plasma Colloid Osmotic Pressure in Pathological Conditions with Special Reference to Occurrence of Edema. *J. Clin. Investigation*, 12:495, 1933.
327. Muntwyler, E.: Clinical Significance of Serum Protein (Albumin and Globulin) Changes. *J. Lab. & Clin. Med.*, 30:526, 1945.
328. Murphy, W. A.: Study of Albuminuria in Applicants for Naval Enlistment. *U. S. Nav. M. Bull.*, 43:321, 1944.
329. Myers, W. K. and Taylor, F. H. L.: Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins. Study of One Case. *J.A.M.A.*, 101:198, 1933.
330. Myers, W. K. and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver. *Arch. Int. Med.*, 55:349, 1935.
331. Napier, L. E.: Tropical Macrocytic Anaemia. *Lancet*, 2:679, 1936.
332. Napier, L. E.: Aetiology of Tropical Macrocytic Anaemia. *Indian M. Gaz.*, 74:1, 1939.
333. Nixon, W. C. W.: Diet in Pregnancy (William Blair Bell Memorial Lecture). *J. Obst. & Gynaec. Brit. Emp.*, 49:614, 1942.

334. von Noorden, C.: Clinical Treatises on the Pathology and Therapy of Disorders of Metabolism and Nutrition. New York: E. B. Treat & Company, 1907.
335. Oelgoetz, A. W., Oelgoetz, P. A. and Wittekind, J.: Protein Insufficiency of Clinical Importance in Surgery on the Liver. *Ohio State M. J.*, 33:643, 1937.
336. Orten, A. U. and Orten, J. M.: A Comparison of the Hematopoietic Values of Certain Dietary Proteins. *Fed. Proc.* 2:67, 1943.
337. Orten, A. U. and Orten, J. M.: The Role of a Dietary Protein in Hemoglobin Formation. *J. Nutrition*, 26:21, 1943.
338. Orten, J. M. and Orten, A. U.: The Hematopoietic Value of Certain Dietary Proteins in the Hemorrhagic Anemia of the Rat. *Fed. Proc.*, 3:95, 1944.
339. Orten, J. M. and Orten, A. U.: The Production of Polycythemia by Cobalt in Rats Made Anemic by a Diet Low in Protein. *Am. J. Physiol.*, 144:464, 1945.
340. Orten, A. U. and Orten, J. M.: A Study of Hemoglobin Formation Following the Administration of Certain Amino Acids to Rats Fed a Diet Low in Protein. *J. Nutrition*, 30:137, 1945.
341. Palmer, R. S.: Functional Albuminuria. *J.A.M.A.*, 96:1559, 1931.
342. Perlman, I., Stillman, N. and Chaikoff, I. L.: Radioactive Phosphorus as Indicator of Phospholipid Metabolism: Further Observations on Effect of Amino-Acids in Phospholipid Activity of Liver. *J. Biol. Chem.*, 135:359, 1940.
343. Peters, J. P., Wakeman, A. M. and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition. *J. Clin. Investigation*, 3:491, 1927.
344. Peters, J. P., et al.: Plasma Proteins in Relation to Blood Hydration. Serum Proteins in Nephritic Edema. *J. Clin. Investigation*, 10:941, 1931.
345. Peters, J. P. et al.: Plasma Proteins in Relation to Blood Hydration. Note on Proteins in Acute Nephritis. *J. Clin. Investigation*, 11:97, 1932.
346. Peters, J. P. et al.: Plasma Proteins in Relation to Blood Hydration. Serum Proteins in Terminal Stages of Renal Disease. *J. Clin. Investigation*, 11:113, 1932.
347. Peters, J. P. and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys. *Am. J. M. Sc.*, 186:808, 1933.
348. Peters, J. P.: Serum Proteins in Health and Disease. *J. Mt. Sinai Hosp.*, 9:127, 1942.
349. Peters, J. P.: Problems of Nitrogen Metabolism. *Fed. Proc.*, 3:197, 1944.
350. Pommerenke, W. T., Slavin, H. B., Kariher, D. H. and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet. Systematic Standardization of Food Proteins for Potency in Protein Regeneration. Fasting and Iron Feeding. *J. Exper. Med.*, 61:261, 1935.
351. Pommerenke, W. T., Slavin, H. B., Kariher, D. H. and Whipple, G. H.: Dog Plasma Protein Given by Vein Utilized in Body Metabolism of Dog. Horse Plasma and Dog Hemoglobin Not Similarly Utilized. *J. Exper. Med.*, 61:283, 1935.
352. Post, J. and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: Relation to Prognosis and to Formation of Ascites. *Arch. Int. Med.*, 69:67, 1942.
353. Post, J. and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: Nitrogen Balance Studies on Five Patients. *Arch. Int. Med.*, 69:83, 1942.
354. Post, W. E. and Thomas, W. A.: Orthostatic Albuminuria. *J.A.M.A.*, 80:293, 1923.
355. Prince, C. L.: Orthostatic Albuminuria. *J. Urol.*, 50:608, 1943.
356. Rafsky, H. A., Bernhard, A. and Rohdenburg, G. L.: Studies in Hypertension. 1. The Production of Experimental Hypertension and a Correlated Effect Upon the Nitrogen Distribution of the Blood Proteins. *Am. J. M. Sc.*, 190:187, 1935.
357. Rasmussen, L. H., Abels, J. C., Pack, G. T. and Rhoads, C. P.: Metabolic Studies on Patients with Cancer of the Gastrointestinal Tract. XIV. The Effects of High Protein Diets on the Prevention of Postoperative Hypoproteinemia in Patients with Gastric Cancer. *J.A.M.A.*, 124:358, 1944.
358. Ratner, B. and Gruchl, H. L.: Passage of Native Proteins Through the Normal Gastrointestinal Wall. *J. Clin. Investigation*, 13:517, 1934.
359. Ratner, S., Rittenberg, D., Keston, A. S. and Schoenheimer, R.: Studies in Protein Metabolism. Chemical Interaction of Dietary Glycine and Body Proteins in Rats. *J. Biol. Chem.*, 134:665, 1940.
360. Ravdin, I. S., Stengel, A., Jr. and Prushankin, M.: Control of Hypoproteinemia in Surgical Patients. *J.A.M.A.*, 114:117, 1940.
361. Ravdin, I. S., Thorogood, E., Riegel, C., Peters, R. and Rhoads, J. E.: The Prevention of Liver Damage and the Facilitation of Repair of the Liver by Diet. *J.A.M.A.*, 121:122, 1943.
362. Ravdin, I. S., McNamee, H. G., Kamholz, J. H. and Rhoads, J. E.: Effect of Hypoproteinemia on Susceptibility to Shock Resulting from Hemorrhage. *Arch. Surg.*, 48:491, 1944.
363. Reimann, H. A., Medes, G. and Fisher, L.: Origin of Blood Proteins. *Folia haematol.*, 52:187, 1934.
364. Rennie, J. B.: Note on Serum Proteins in Normal Infants and Children. *Arch. Dis. Childhood*, 10:415, 1935.
365. Rhoads, J. E., Fliegelman, M. T. and Panzer, L. M.: Mechanism of Delayed Wound Healing in the Presence of Hypoproteinemia. *J.A.M.A.*, 118:21, 1942.
366. Rhoads, J. E. and Kasinskas, W.: Influence of Hypoproteinemia on Formation of Callus in Experimental Fracture. *Surgery*, 11:38, 1942.
367. Richards, M. B.: Dietary Factor in Reproduction and Lactation. *Brit. M. J.*, 2:418, 1943.
368. Richter, C. P.: The Nutritional Value of Some Common Carbohydrates, Fats and Proteins Studied in Rats by the Single Food Choice Method. *Am. J. Physiol.*, 133:29, 1941.
369. Richter, C. P. and Rice, K. K.: Comparison of the Nutritive Value of Dextrose and Casein and of the Effects Produced on Their Utilization by Thiamine. *Am. J. Physiol.*, 141:346, 1944.
370. Richter, C. P., Schmidt, E. C. H., Jr. and Malone, P. D.: Further Observations on the Self-Regulatory Dietary Selections of Rats Made Diabetic by Pancreatectomy. *Bull. Johns Hopkins Hosp.*, 76:192, 1945.
371. Riggs, E., et al.: A Nutrition Survey in East York Township. Description of Survey and General Statement of Results. *Canad. J. Pub. Health*, 34:193, 1943.
372. Rimmerman, A. B., Schwartz, S. O., Popper, H. and Steigmann, F.: Dietary Factors in Treatment of Cirrhosis Without Jaundice. *Am. J. Digest. Dis.*, 11:401, 1944.
373. Robertson, E. C. and Tisdall, F. F.: Nutrition and Resistance to Disease. *Canad. M. A. J.*, 40:282, 1939.
374. Robinson, H. W., Price, J. W. and Hogden, C. G.: Estimation of Albumin and Globulin in Blood Serum. Study of Errors Involved in Filtration Procedure. *J. Biol. Chem.*, 120:481, 1937.
375. Robschheit-Robbins, F. S. and Whipple, G. H.: Reserve Store of Hemoglobin Producing Substances in Growing Dogs as Influenced by Diet. *Am. J. Physiol.*, 112:27, 1935.
376. Robschheit-Robbins, F. S., Walden, G. B. and Whipple, G. H.: Blood Regeneration in Severe Anemia. Fractions of Kidney, Spleen and Heart Compared with Standard Liver Fractions. *Am. J. Physiol.*, 113:467, 1935.
377. Robschheit-Robbins, F. S., Madden, S. C., Rowe, A. P., Turner, A. P. and Whipple, G. H.: Hemoglobin and Plasma Protein. Simultaneous Production During Continued Bleeding as Influenced by Diet Protein and Other Factors. *J. Exper. Med.*, 72:479, 1940.
378. Robschheit-Robbins, F. S., Miller, L. L. and Whipple, G. H.: Hemoglobin and Plasma Protein. Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma, Hemoglobin, and Digests of Serum, Hemoglobin, and Casein. *J. Exper. Med.*, 77:375, 1943.
379. Rodriguez-Molina, R.: Tropical Macrocytic Anemia in Puerto Rico. Report of Two Cases. *Puerto Rico J. Pub. Health & Trop. Med.*, 15:177, 1939.
380. Rose, M. S.: The Foundations of Nutrition. New York: Macmillan Company, 1933.
381. Rose, W. C.: The Nutritive Significance of the Amino Acids and Certain Related Compounds. *Science*, 86:298, 1937.
382. Rose, W. C.: The Nutritive Significance of Amino Acids. *Physiol. Rev.*, 18:109, 1938.
383. Rose, W. C.: Physiology of Amino Acid Metabolism (Ludwig Hektoen Lecture). *Proc. Inst. Med. Chicago*, 12:98, 1918.
384. Rose, W. C. and Rice, E. E.: The Significance of the Amino Acids in Canine Nutrition. *Science*, 90:186, 1939.
385. Rose, W. C., Haines, W. J. and Johnson, J. E.: The Role of the Amino Acids in Human Nutrition. *J. Biol. Chem.*, 146:683, 1942.
386. Rose, W. C., Haines, W. J., Johnson, J. E. and Warner, D. T.: Further Experiments on the Role of Amino Acids in Human Nutrition. *J. Biol. Chem.*, 148:457, 1943.
387. Rose, W. C.: Role of Protein in Diet. *Proc. Inst. Med. Chicago*, 15:24, 1944.
388. Ross, W. F. and Christensen, H. N.: Carbon Suboxide and Proteins. I. The Nature of the Reaction. *J. Biol. Chem.*, 137:89, 1941.

389. Ross, W. F. and Green, L. S.: Carbon Suboxide and Proteins. III. The Reaction of Carbon Suboxide with Amino Acids. *J. Biol. Chem.*, 137:105, 1941.
390. Sachar, L. A., Horvitz, A. and Elman, R.: Studies on Hypoalbuminemia Produced by Protein-Deficient Diets. Hypoalbuminemia as a Quantitative Measure of Tissue Protein Depletion. *J. Exper. Med.*, 75:453, 1942.
391. Sahyun, M. and Webster, G.: The Influence of Arterenal and Epinephrine on the Distribution of Glycogen in Rats. *Arch. internat. de pharmacodyn. et de therap.*, 45:291, 1933.
392. Sahyun, M.: Some Aspects of Metabolism Following Parenteral Administration of Casein Hydrolysate. *Proc. Soc. Exper. Biol. & Med.*, 48:14, 1941.
393. Sahyun, M., editor: *Outline of the Amino Acids and Proteins*. New York: Reinhold Publishing Corporation, 1944.
394. Sahyun, M.: The Nutritional Significance of Amino Acids and Proteins. *Am. J. Digest. Dis.*, 12:80, 1945.
395. Sako, W.: Resistance to Infection as Affected by Variations in the Proportions of Protein, Fat, and Carbohydrate in the Diet. Experimental Study. *J. Pediat.*, 20:475, 1942.
396. Scatchard, G., Batchelder, A. C. and Brown, A.: Osmotic Pressure of Plasma and of Serum Albumin. *J. Clin. Investigation*, 23:458, 1944.
397. Schmidt, C. L. A., editor: *The Chemistry of the Amino Acids and Proteins*. Springfield, Illinois: C. C. Thomas, 1938.
398. Schoenheimer, R., Ratner, S., Rittenberg, D. and Heidelberger, M.: Interaction of Blood Proteins of Rats with Dietary Nitrogen. *J. Biol. Chem.*, 144:541, 1942.
399. Schoenheimer, R., Ratner, S., Rittenberg, D. and Heidelberger, M.: Interaction of Antibody Protein with Dietary Nitrogen in Actively Immunized Animals. *J. Biol. Chem.*, 144:545, 1942.
400. Schweigert, B. S., Tatman, I. E. and Elvehjem, C. A.: The Leucine, Valine, and Isoleucine Content of Meats. *Arch. Biochem.*, 6:177, 1945.
401. Seaman, B. W. and Ponder, E.: Estimation and Control of Postoperative Dehydration with Aid of Hemoglobin and Plasma Protein Determinations. *J. Clin. Investigation*, 22:673, 1943.
402. Seeley, R. D.: Nitrogen Balance and Plasma Protein Regeneration in Hypoproteinemic Dogs. *Am. J. Physiol.*, 144:369, 1945.
403. Shaffer, P. A. and Coleman, W.: Protein Metabolism in Typhoid Fever. *Arch. Int. Med.*, 4:538, 1909.
404. Shaffroff, B. G. P., Barcham, I. S. and Doubilet, H.: Clinical Use of a Red Cell Amino Acid Mixture as a Substitute for Whole Blood Transfusions. *Am. J. Surg.*, 68:348, 1945.
405. Shearburn, E. W.: Effect of Plasma Transfusion upon Serum Proteins and Blood Volume of Dogs Rendered Hypoproteinemic by Diet. *Surg., Gynec. & Obst.*, 74:343, 1942.
406. Shelburne, S. A. and Egloff, W. C.: Experimental Edema. *Arch. Int. Med.*, 48:51, 1931.
407. Sherman, H. C., Gillett, L. H. and Osterberg, E.: The Protein Requirements of Maintenance in Man and the Nutritive Efficiency of Bread Protein. *J. Biol. Chem.*, 41:97, 1920.
408. Sherman, H. C.: *The Chemistry of Foods and Nutrition*. New York: Macmillan Company, 1941.
409. Sherman, H. C.: *The Science of Nutrition*. New York: Columbia University Press, 1943.
410. Shohl, A. T., Butler, A. M., Blackfan, K. D. and MacLachlan, E.: Nitrogen Metabolism During the Oral and Parenteral Administration of the Amino-Acids of Hydrolyzed Casein. *J. Pediat.*, 15:469, 1939.
411. Shohl, A. T. and Blackfan, K. D.: The Intravenous Administration of Crystalline Amino Acids to Infants. *J. Nutrition*, 20:305, 1940.
412. Shohl, A. T.: Nitrogen Storage Following Intravenous and Oral Administration of Casein Hydrolysate to Infants with Acute Gastrointestinal Disturbance. *J. Clin. Investigation*, 22:257, 1943.
413. Shohl, A. T., May, C. D. and Shwachman, H.: Studies of Nitrogen and Fat Metabolism of Infants and Children with Pancreatic Fibrosis. *J. Pediat.*, 23:267, 1943.
414. Smith, H. P., Belt, A. E. and Whipple, G. H.: Rapid Blood Plasma Protein Depletion and Curve of Regeneration. *Am. J. Physiol.*, 52:54, 1920.
415. Spies, T. D.: *Diagnosis and Principles of Treatment of Dietary Deficiency Diseases*. Texas State J. Med., 38:427, 1942.
416. Spies, T. D., Vilter, R. W. and Douglas, G., Jr.: Nutrition in Convalescence and Rehabilitation. *South. M. J.*, 37:560, 1944.
417. Stare, F. J. and Thorn, G. W.: Some Medical Aspects of Protein Foods. *Am. J. Pub. Health*, 33:1444, 1943.
418. Stare, F. J. and Davidson, C. S.: Protein: Its Role in Human Nutrition. Introduction. *J.A.M.A.*, 127:985, 1945.
419. Stare, F. J. and Thorn, G. W.: Protein Nutrition in Problems of Medical Interest. *J.A.M.A.*, 127:1120, 1945.
420. Stengel, A., Jr. and Ravdin, I. S.: The Maintenance of Nutrition in Surgical Patients with a Description of the Orojejunal Method of Feeding. *Surgery*, 6:511, 1939.
421. Stewart, J. N.: Correction of Hypoproteinemia. *J. Am. Osteopath A.*, 44:480, 1945.
422. Stiebling, H. K. and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities. Circular No. 507, U. S. Dept. Agric., Washington, 1939.
423. Strauss, M. B. and Castle, W. B.: Studies of Anemia in Pregnancy. Relationship of Dietary Deficiency and Gastric Secretion to Blood Formation During Pregnancy. *Am. J. M. Sc.*, 184:663, 1932.
424. Strauss, M. B. and Castle, W. B.: Studies of Anemia in Pregnancy. III. The Etiologic Relationship of Gastric Secretory Defects and Dietary Deficiency to the Hypochromic and Macrocytic (Pernicious) Anemias of Pregnancy and the Treatment of These Conditions. *Am. J. M. Sc.*, 185:539, 1933.
425. Strauss, M. B. and McDonald, W. J.: Polyneuritis of Pregnancy. Dietary Deficiency Disorder. *J.A.M.A.*, 100:1320, 1933.
426. Strauss, M. B.: Observations on the Etiology of the Toxemias of Pregnancy. The Relationship of Nutritional Deficiency, Hypoproteinemia, and Elevated Venous Pressure to Water Retention in Pregnancy. *Am. J. M. Sc.*, 190:811, 1935.
427. Strauss, M. B.: Observations on the Etiology of the Toxemias of Pregnancy. Production of Acute Exacerbation of Toxemia by Sodium Salts in Pregnant Women with Hypoproteinemia. *Am. J. M. Sc.*, 194:772, 1937.
428. Strauss, M. B.: Observations on Etiology of Toxemias of Pregnancy. Primary Role of Plasma Proteins in Conditioning Water Retention and Edema Formation in Normal and "Toxic" Pregnancy. *Am. J. M. Sc.*, 195:723, 1938.
429. Sturgis, C. C. and Farrar, G. E., Jr.: Hemoglobin Regeneration in the Chronic Hemorrhagic Anemia in Dogs. I. The Effect of Iron and Protein Feeding. *J. Exper. Med.*, 62:457, 1935.
430. Swaminathan, M.: The Relative Value of the Proteins of Certain Foodstuffs in Nutrition. General Conclusions. *Indian J. M. Research*, 26:113, 1938.
431. Swanson, L. W. and Greene, J. A.: Further Observations on the Role of Diet in the Etiology and Treatment of Spontaneous Hypoglycemia. *J. Lab. & Clin. Med.*, 26:828, 1941.
432. Sweigert, C. F.: Multiple Myeloma with Hypoproteinemia. Case Report. *Am. J. M. Sc.*, 190:245, 1935.
433. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., Browder, N. C. and Lund, C. C.: Problems of Protein Nutrition in Burned Patients. *Ann. Surg.*, 118:215, 1943.
434. Taylor, F. H. L., Levenson, S. M., Davidson, C. S. and Adams, M. A.: Abnormal Nitrogen Metabolism in Patients with Thermal Burns. *New England J. Med.*, 229:855, 1943.
435. Taylor, F. H. L., Levenson, S. M., Davidson, C. S., Adams, M. A. and MacDonald, H.: Abnormal Nitrogen Metabolism in Burns. *Science*, 97:423, 1943.
436. Taylor, F. H. L., Davidson, C. S. and Levenson, S. M.: Problem of Nutrition in Presence of Excessive Nitrogen Requirement in Seriously Ill Patients with Particular Reference to Thermal Burns. *Connecticut M. J.*, 8:141, 1944.
437. Taylor, F. H. L.: Nitrogen Requirement of Patients with Thermal Burns. *J. Indust. Hyg. & Toxicol.*, 26:152, 1944.
438. Taylor, G. F. and Chhuttani, P. N.: Nutritional Macrocytic Anaemia and the Animal Protein of Diet. *Brit. M. J.*, June 9, 1945, p. 800.
439. Thompson, W. D., Ravdin, I. S. and Frank, I. L.: Effect of Hypoproteinemia on Wound Disruption. *Arch. Surg.*, 36:500, 1938.
440. Thompson, W. D., Ravdin, I. S., Rhoads, J. E. and Frank, I. L.: Use of Lyophile Plasma in the Correction of Hypoproteinemia and the Prevention of Wound Disruption. *Arch. Surg.*, 36:509, 1938.
441. Thompson, W. H., McQuarrie, I. and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver: With Studies of Water and Mineral Exchanges. *J. Pediat.*, 9:604, 1936.
442. Thorn, G. W., Quinby, J. T. and Clinton, M., Jr.: A Comparison of the Metabolic Effects of Isocaloric Meals of Varying Composition, with Special Reference to the Prevention of Postprandial Hypoglycemic Symptoms. *Ann. Int. Med.*, 18:913, 1943.
443. Thornton, T. F., Jr., Adams, W. E. and Schafer, P. W.: Hypoproteinemia in Thoracic Surgery: A Clinical Study. *Surg., Gynec. & Obst.*, 79:368, 1944.
444. Thorp, E. G. and Wakefield, E. G.: Orthostatic Albuminuria. Comparison with Other Types of Albuminuria. *Ann. Int. Med.*, 6:1565, 1933.
445. Tompkins, W. T.: Significance of Nutritional Deficiency in Pregnancy. Preliminary Report. *J. Internat. Coll. Surgeons*, 4:147, 1941.

446. Totter, J. R. and Day, P. L.: Cataract and Other Ocular Changes Resulting from Tryptophane Deficiency. *J. Nutrition*, 24:159, 1942.
447. Trowell, H. C.: Deficiency Anaemias of Malnutrition. *Lancet*, 1:43, 1943.
448. Tucker, H. F. and Eckstein, H. C.: The Effect of Supplementary Methionine and Cystine on the Production of Fatty Livers by Diet. *J. Biol. Chem.*, 121:479, 1937.
449. Tumen, H. and Bockus, H. L.: Clinical Significance of Serum Proteins in Hepatic Diseases Compared with Other Liver Function Tests. *Am. J. M. Sc.*, 193:788, 1937.
450. Turner, D. F.: Selection of Protein Containing Foods to Meet Protein Requirements. *J.A.M.A.*, 128:590, 1945.
451. Ungley, C. C.: Some Deficiencies of Nutrition and Their Relation to Disease (Goulstonian Lecture). *Lancet*, 1:875, 925, 981, 1938.
452. Vaughn, M. and Mitchell, H. S.: A Continuation of a Nutrition Project in Northern Newfoundland. *J. Am. Dietet. A.*, 8:526, 1933.
453. Wainio, W. W.: The Thiamine Requirement of the Albino Rat as Influenced by the Substitution of Protein for Carbohydrate in the Diet. *J. Nutrition*, 24:317, 1942.
454. Wait, B. and Roberts, L. J.: Studies in the Food Requirement of Adolescent Girls. The Protein Intake of Well Nourished Girls 10 to 16 Years of Age. *J. Am. Dietet. A.*, 8:403, 1933.
455. Wang, C. C., Kern, R. and Kaucher, M.: Metabolism of Undernourished Children. A Study of the Basal Metabolism, Caloric Balance and Protein Metabolism During a Period of Gain in Weight. *Am. J. Dis. Child.*, 38:476, 1929.
456. Warkany, J. and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency. VI. The Preventive Factor. *J. Nutrition*, 27:477, 1944.
457. Warren, J. V. and Stead, E. A., Jr.: Protein Content of Edema Fluid in Patients with Acute Glomerulonephritis. *Am. J. M. Sc.*, 208:618, 1944.
458. Waters, W. C., Jr.: Spontaneous Hypoglycemia: The Role of Diet in Etiology and Treatment. *South. M. J.*, 24:249, 1931.
459. Watson, M.: Studies on the Influence of Diet on Resistance to Infection. I. The Effect of Various Diets on Fertility, Growth and Survival of Mice. *J. Hyg.*, 37:396, 1937.
460. Watson, M.: Studies on the Influence of Diet on Resistance to Infection. II. The Effect of Various Diets on the Resistance of Mice to Bacterial Infection. *J. Hyg.*, 37:420, 1937.
461. Watson, M., Wilson, J. and Topley, W. W. C.: The Effect of Diet on Epidemics of Mouse Typhoid. *J. Hyg.*, 38:424, 1938.
462. Weech, A. A. and Ling, S. M.: Nutritional Edema. Observations on Relations of Serum Proteins to Occurrence of Edema and to Effect of Certain Inorganic Salts. *J. Clin. Investigation*, 10:869, 1931.
463. Weech, A. A., Snellings, C. E. and Goettsch, E.: Relation Between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on Protein Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis. *J. Clin. Investigation*, 12:193, 1933.
464. Weech, A. A., Goettsch, E. and Reeves, E. B.: The Effect of Serum Transfusion on the Plasma Protein Depletion Associated with Nutritional Edema in Dogs. *J. Clin. Investigation*, 12:217, 1933.
465. Weech, A. A., Goettsch, E. and Reeves, E. B.: Proteins of Blood and Subcutaneous Lymph in Dogs. *J. Clin. Investigation*, 12:1021, 1933.
466. Weech, A. A., Goettsch, E. and Reeves, E. B.: Nutritional Edema in the Dog. I. Development of Hypoproteinemia on a Diet Deficient in Protein. *J. Exper. Med.*, 61:299, 1935.
467. Weech, A. A., Goettsch, E. and Reeves, E. B.: Nutritional Edema in the Dog. II. Hypoalbuminemia and the Augmentation of Tissue Fluid. *J. Exper. Med.*, 61:717, 1935.
468. Weech, A. A., Reeves, E. B. and Goettsch, E.: The Relationship Between the Specific Gravity and Protein Content in Plasma, Serum, and Transudate from Dogs. *J. Biol. Chem.*, 113:167, 1936.
469. Weech, A. A. and Paige, B. H.: Nutritional Edema in the Dog. IV. Peptic Ulcer Produced by the Same Low Protein Diet That Leads to Hypoproteinemia and Edema. *Am. J. Path.*, 13:249, 1937.
470. Weech, A. A., Wollstein, M. and Goettsch, E.: Nutritional Edema in the Dog. V. Development of Deficits in Erythrocytes and Hemoglobin on a Diet Deficient in Protein. *J. Clin. Investigation*, 16:719, 1937.
471. Weech, A. A. and Goettsch, E.: Dietary Protein and the Regeneration of Serum Albumin. I. Method of Assay and Discussion of Principles. *Bull. Johns Hopkins Hosp.*, 63:154, 1938.
472. Weech, A. A. and Goettsch, E.: Dietary Protein and the Regeneration of Serum Albumin. II. Comparison of the Potency Values of Beef Serum, Beef Muscle and Casein. *Bull. Johns Hopkins Hosp.*, 63:181, 1938.
473. Weech, A. A.: The Significance of the Albumin Fraction of the Serum. Harvey Lecture. *Bull. New York Acad. Med.*, 15:63, 1939.
474. Weech, A. A.: Puzzles of Protein Privation: A Decade of Research into the Biologic Effects of Restricted Dietary Protein. *J. Pediatr.*, 19:608, 1941.
475. Weiner, D. O., Rowlette, A. P. and Elman, R.: Significance of Loss of Serum Protein in Therapy of Severe Burns. *Proc. Soc. Exper. Biol. & Med.*, 34:484, 1936.
476. Welch, A. de M.: The Preparation of a Casein Hydrolysate for the Study of the Relationship Between Choline and Homocystine. *J. Biol. Chem.*, 137:173, 1941.
477. Whipple, A. O.: Critical Latent or Lag Period in Healing of Wounds. *Ann. Surg.*, 112:481, 1940.
478. Whipple, G. H., Smith, H. P. and Belt, A. E.: Shock as a Manifestation of Tissue Injury Following Rapid Plasma Protein Depletion. The Stabilizing Value of Plasma Proteins. *Am. J. Physiol.*, 52:72, 1920-1921.
479. Whipple, G. H.: Hemoglobin Construction Without Body as Influenced by Diet Factors. Consideration of Anemia Problems. *Am. J. M. Sc.*, 175:721, 1938.
480. Whipple, G. H.: Hemoglobin Regeneration As Influenced by Diet and Other Factors. Nobel Prize Lecture. *J.A.M.A.*, 104:791, 1935.
481. Whipple, G. H. and Robscheit-Robbins, F. S.: Control Basal Diets in Anemic Dogs. Method Factors and Hemoglobin Production. *Am. J. Physiol.*, 115:651, 1936.
482. Whipple, G. H. and Robscheit-Robbins, F. S.: Amino Acids (Natural and Synthetic) As Influencing Hemoglobin Production in Anemia. *Proc. Soc. Exper. Biol. & Med.*, 36:629, 1937.
483. Whipple, G. H.: Protein Production and Exchange in the Body Including Hemoglobin, Plasma Protein and Cell Protein. *Am. J. M. Sc.*, 196:609, 1938.
484. Whipple, G. H. and Robscheit-Robbins, F. S.: Amino Acids and Hemoglobin Production in Anemia. *J. Exper. Med.*, 71:569, 1940.
485. Whipple, G. H.: Blood Plasma Proteins. Editorial. *Surg. Gynec. & Obst.*, 73:886, 1941.
486. Whipple, G. H.: Hemoglobin and Plasma Proteins: Their Production, Utilization and Interrelation. *Am. J. M. Sc.*, 203:477, 1942.
487. Whipple, G. H.: The Production, Utilization and Interrelation of Blood Proteins—Hemoglobin and Plasma Proteins. Pasteur Lecture. *Proc. Inst. Med. Chicago*, 14:2, 1942.
488. Whipple, G. H., Robscheit-Robbins, F. S. and Hawkins, W. B.: Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron. *J. Exper. Med.*, 81:171, 1945.
489. White, J. and Andervont, H. B.: Effect of Diet Relatively Low in Cystine on Production of Spontaneous Mammary-Gland Tumors in Strain C3H Female Mice. *J. Nat. Cancer Inst.*, 3:449, 1943.
490. Wies, C. H. and Peters, J. P.: Osmotic Pressure of Proteins in Whole Serum. *J. Clin. Investigation*, 16:93, 1937.
491. Williams, P. F. and Fralin, F. G.: Nutrition Study in Pregnancy. Dietary Analyses of Seven-Day Food Intake Records of 514 Pregnant Women, Comparison of Actual Food Intake with Various Stated Requirements, and Relationship of Food Intake to Various Obstetric Factors. *Am. J. Obst. & Gynec.*, 41:1, 1942.
492. Williams, P. F.: Importance of Adequate Protein Nutrition in Pregnancy. *J.A.M.A.*, 127:1052, 1945.
493. Wilson, K. M.: Nitrogen Metabolism During Pregnancy. *Bull. Johns Hopkins Hosp.*, 27:121, 1916.
494. Wilson, S. J. and Walzer, M.: Absorption of Undigested Protein in Human Beings. IV. Absorption of Unaltered Egg Proteins in Infants and Children. *Am. J. Dis. Child.*, 50:49, 1935.
495. Wolman, I. J.: The Incidence, Causes and Intermittency of Proteinuria in Young Men. *Am. J. M. Sc.*, 210:86, 1943.
496. Womack, M., Kemmerer, K. S. and Rose, W. C.: The Relation of Methionine and Cystine to Growth. *J. Biol. Chem.*, 121:403, 1937.
497. Womack, M. and Rose, W. C.: The Partial Replacement of Dietary Methionine by Cystine for Purposes of Growth. *J. Biol. Chem.*, 141:375, 1941.
498. Wright, G. G.: Studies on the Denaturation of Antibody. II. The Effect of Protein Concentration on the Rate of Denaturation of Diphtheria Antitoxin by Urea. *J. Exper. Med.*, 81:447, 1945.
499. Wright, L. D., Skeggs, H. R. and Sprague, K. L.: The Effect of Feeding Succinylsulfathiazole to Rats Receiving Purified

- Diets High in Carbohydrate, Protein, Fat, or Protein and Fat. *J. Nutrition*, 29 431, 1945.
500. Youmans, J B, Bell, A and Frank, H Endemic Nutritional Edema Clinical Findings and Dietary Studies *Arch Int. Med*, 50 843, 1932.
501. Youmans, J B. Endemic Edema *JAMA*, 99 883, 1932
502. Youmans, J B and Patton, E W. Nutritional Deficiencies Diagnosis and Treatment. Lippincott, 1943
503. Youmans, J B, Patton, E W. and Kern, R Surveys of the Nutrition of Populations, Description of the Population, General Methods and Procedures, and the Findings in Respect to the Energy Principle (Calories) in a Rural Population in Middle Tennessee. *Am J Pub Health*, 32 1371, 1942, 33-58, 1943.
504. Youmans, J B, Patton, E W, Sutton, W. R, Kern, R and Steinkamp, R Surveys of the Nutrition of Populations II. The Protein Nutrition of a Rural Population in Middle Tennessee *Am J Pub. Health*, 33 955, 1943
505. Youmans, J B The Clinical Detection of Protein Deficiency. *JAMA*, 128 439, 1945.
506. Yuile, C L and Knutti, R E Blood Plasma Proteins as Influenced by Intravenous Injection of Gum Acacia Production of Chronic Hypoproteinemia *J Exper Med*, 70 605, 1939
507. Zeldis, L J, Alling, E L, McCoord, A B and Kulka, J P Plasma Protein Metabolism—Electrophoretic Studies Chronic Depletion of Circulating Proteins During Low Protein Feeding *J Exper Med*, 82 157, 1945
508. Zimmer, R, Weill, J and Dubois, M The Nutritional Situation in the Camps of the Unoccupied Zone in France in 1941 and 1942 and Its Consequences *New England J Med*, 230 303, 1944.
509. Report on Physiological Bases of Nutrition League of Nations Health Comm. Tech Commission, London, 1935
510. Nutrition of Expectant and Nursing Mothers Interim Report of the People's League of Health *Lancet*, 2 10, 1942, *Brit. M J*, 2 77, 1942, *M Officer*, 68 20, 1942
511. Editorial Postoperative Nitrogen Loss *JAMA*, 121 346, 1943.
512. Food and Nutrition Board of the National Research Council Reprint and Circular Series, No 115, January 1943
513. Report of the Committee on Food Habits 1941-1943. The Problem of Changing Food Habits Bulletin of the National Research Council, No 108, October 1943
514. Inadequate Diets and Nutritional Deficiencies in the United States Their Prevalence and Significance Bulletin 109, National Research Council, November 1943
515. Cabor Case 30031 *New England J Med*, 230 82, 1944
516. Effects of Nutrition on Phagocytosis *Nutrition Rev*, 2 232, 1944
517. Malnutrition During Convalescence Prepared under direction of the Committee on Convalescence and Rehabilitation of the National Research Council *War Med*, 6 1, 1944
518. Anon Proteins and Amino Acids *Am Professional Pharmacist*, 11 515, 1945
519. Editorial Treatment of Infective Hepatitis *Brit M J*, 1 415, 1945
520. Editorial Treatment of Severe Starvation *Brit M J*, 1 614, 1945
521. Editorial Nutritional Diarrhoea *Brit M J*, 2 258, 1945
522. Editorial Nutrition and Cancer *JAMA*, 128 594, 1945.
523. Editorial Protein in Illness *Lancet*, 1 309, 1945
524. Editorial The Use of Protein Hydrolysates (Amino Acids) and of Transudate Fluid in the Replacement Therapy of Chronic Protein Deficiencies *Rev Gastroenterol*, 12 209, 1945

Abdominal Pain In Pneumonia

By

HARRY GAUSS, M.D.

DENVER, COLORADO

REFERRED abdominal pain sometimes occurs in pneumonia. When it is present, it becomes an important symptom because it focuses attention on the digestive tract, thereby tending to cause errors in diagnosis.

Thoracic pain occurs in eighty percent of patients with pneumonia, while abdominal pain occurs in eight percent of these patients, according to Chatard (1).

The appearance of thoracic pain in the early stages of pneumonia is a helpful sign, because it directs attention to the respiratory tract, thereby aiding in the interpretation of the disease process; while the appearance of abdominal pain distracts attention from the pulmonary tract and focuses it on the digestive tract, and so may give rise to confusion.

Thoracic pain bears a definite embryologic, anatomic and neurologic relationship to pneumonia, hence its appearance is to be anticipated; but abdominal pain bears none of these relationships. Its appearance is a physiologic surprise and it becomes a problem for study and consideration.

Although abdominal pain occurs in about eight percent of patients with pneumonia, yet in most of them the abdominal distress presents little diagnostic difficulty for it is easily recognized as a functional dyspepsia resulting from the toxemia. The dyspeptic

symptoms commonly encountered are loss of appetite, diffuse abdominal pain, meteorism, distention, flatulence, distress after eating, constipation, sometimes nausea and vomiting.

However occasionally, the abdominal pain and other associated symptoms may be so violent as to overshadow the thoracic symptoms. In these cases the digestive symptoms may become so pronounced and so sharply localized that they may simulate acute surgical crises of the abdomen, as appendicitis, cholecystitis, peptic ulcer, intestinal obstruction, etc. Indeed several writers have stated that patients with pneumonia have been operated on for supposed appendicitis or other acute surgical crises of the abdomen when the entire syndrome proved to be referred pain from the lungs.

Thus, Brown (2) states that the acute abdomen simulating appendicitis may be met in central pneumonia. Norris (3) states that patients with pneumonia have been seized with such violent abdominal pain accompanied with rigidity of the abdominal muscles that a laparotomy has been performed for supposed appendicitis when the peritoneal cavity proved to be entirely normal and pneumonia was found to be the cause of the abdominal disturbance. Reiman (4) states that the pain in pneumonia may be referred to other parts of the trunk, and may suggest acute appendicitis and unnecessary operations have been performed as a result.

In studying the literature, one finds these and other general statements about the referred pain from pneumonia simulating acute abdominal crises, but the recording of actual cases is rare.

For a number of years, we have been interested in the problem of abdominal pain and its bizarre manifestations. We have long recognized that the abdomen is the barometer of the body, that it tells of trouble but does not always locate it; that the cause of abdominal pain may originate either within or outside of the abdomen; that the severity of the abdominal pain is no index of the location or of the cause which gives rise to it, that the most violent types of abdominal pain may originate from causes either within or outside of the abdomen, and the same holds true for mild types of abdominal distress.

Pneumonia is but one of a number of conditions located outside of the abdomen which is capable of producing digestive disturbances. Among some of the other extra-abdominal causes for abdominal distress mentioned recently in the literature are the following: psychic disturbances, disorders of the central nervous system, diseases of the cardio-vascular system, the onset of pulmonary tuberculosis, disorders of the renal system, diseases in the pelvis, anorectal disease, epilepsy equivalents, etc. Some of these extra-abdominal causes for abdominal pain, we have discussed elsewhere (5, 6, 7, 8, 9, 10).

Pursuing our interest in the bizarre causes of abdominal pain, we have encountered a number of instances of abdominal pain due to pneumonia, where the gastrointestinal tract was found to be essentially normal and the pain apparently had its origin in the pneumonic process.

CASE I. Lobar Pneumonia Simulating Acute Appendicitis. Laparotomy with Recovery.

W. G., a white adult male of 55 years was admitted to the surgical ward of a local hospital because of acute abdominal distress in the right lower quadrant of the abdomen several days in duration. During the past twenty-four hours, the pain had become quite sharp. He was nauseated and he vomited when he attempted to eat. He felt warm, complained of a slight headache.

The abdominal pain had become so sharp that it caused him to lie down with his legs drawn up, in which position he felt less pain.

Physical examination showed a white male, well nourished, acutely ill, weighing 160 pounds, 5 feet 9 inches in height; his temperature was 102, his pulse was 100, his respiration 22, his blood pressure 110/64.

The heart borders were normal, the rate rapid, the tones were clear. The lungs were resonant, the breath sounds were somewhat roughened at both bases, however there was no distinct area of dullness in evidence.

The abdomen was quite tense and did not relax well. The muscles in the right lower quadrant were board like in hardness, and there was distinct tenderness in McBurney's region. The liver and spleen were not palpable. The reflexes were present, equal and exaggerated.

Examination of the blood showed the R.B.C. to be 5,640,000; the W.B.C. was 27,000; the hemoglobin was 84%, the differential count was polys 82%, lymphs 16%, transitionals 1% and eosinophiles 1%. There was a trace of albumin in the urine, with a few hyalin casts and some W.B.C.'s.

X-ray examinations were not made.

A diagnosis of Acute Appendicitis was made.

A laparotomy was advised and performed. The appen-

dix and peritoneum were found to be normal on gross and subsequent microscopic examination.

A few hours after the operation his temperature rose to 104, the patient developed a cough, the respiration became shallow and labored; dullness appeared over the right lower lobe, also there appeared increased voice and tactile fremitus and numerous moist rales. The presence of a lobar pneumonia was evident at this time. Penicillin was given. The clinical course was typical of a lobar pneumonia. Recovery was uneventful.

Comment. Patient W. G. exhibited a syndrome of acute abdominal pain and other symptoms simulating acute appendicitis as an expression of the onset of a lobar pneumonia. The appendix was removed and found to be free of inflammatory changes. The abdominal pain was part of the digestive syndrome originating in the inflamed portion of the right lung. When the pulmonary lesion improved, the digestive symptoms subsided.

CASE II. Lobar Pneumonia Simulating Acute Appendicitis. Laparotomy with Recovery.

Miss D. H., a student nurse in a local hospital, was admitted to the surgical section on May 7 because of diffuse cramp like pains in the abdomen, also she was nauseated, had lost her desire for food, was constipated and ached all over. Later in the day the pain settled in the right lower quadrant of the abdomen as a severe crampy pain which made it impossible for her to continue her duties. Beyond her extreme fatigue and abdominal distress, she had no important symptoms. There was no cough, no pain in the chest, no shortness of breath.

Physical examination showed a white young woman, twenty years of age, weighing 95 pounds, measuring 5 feet in height, apparently acutely ill. Her temperature was 103, her pulse was 120, her respiration was 26, her blood pressure was 96/50.

Her throat was congested. The heart borders were normal, the tones were clear. The lungs were resonant, the breath sounds were vesicular, a few scattered rales were heard.

The abdomen was rigid, tympanitic, with extreme tenderness in McBurney's region. The reflexes were present and equal.

The urine contained a trace of albumen, the white blood count was 12,600 with 89% polys, 9% lymphs and 2% mononuclears.

A diagnosis of Acute Appendicitis was made. Appendectomy was advised and performed. The appendix subsequently, showed no important changes on gross and microscopic examination.

The following day, the patient manifested a cough and complained of pain in the right chest. Examination at this time showed impaired resonance over the right lower lobe, also there was present increased voice fremitus, bronchovesicular breath sounds and numerous moist rales. The signs of consolidation were evident, also the respiration was labored and there was present marked dyspnoea.

The presence of a right lower lobar pneumonia was evident at this time. Sulfathiazole was given. The patient ran a typical pneumonia course. The crisis occurred on the fourth day. Recovery from both the appendectomy and the pneumonia was uneventful.

Comment. Patient D. H. presented a syndrome of abdominal pain and other symptoms suggestive of acute appendicitis as an expression of a right lower lobar pneumonia. The appendix was subsequently found to be free of inflammatory changes. The abdominal symptoms were referred from the pulmonary region. They were functional in character, and subsided with the recession of the pneumonia.

CASE III. Lobar Pneumonia Simulating Intestinal Obstruction.

The following case of abdominal pain in pneumonia simulating intestinal obstruction is of special interest because the abdominal pain occurred on the opposite side to that of the pneumonia. We are indebted to Dr. Wellenweber of Denver for this case report.

Mrs. B. G., a white woman of 70 years, complained of pain in the right lower quadrant of the abdomen. The distress was several days in duration. It was dull and constant in character and very annoying, causing her to

take to her bed and send for her physician. At times the pain became quite sharp and stabbing in character and doubled her up with agony. The pain did not radiate in any particular direction, but remained confined to the right lower quadrant of the abdomen. Nausea was present but no vomiting. She also complained of bloating, belching and flatulence. The pain kept getting worse. The abdomen became distended and tense. All movements became painful. She became constipated and lost her desire for food. Otherwise she had no complaint. She had no cough, no shortness of breath, no pains in the chest. Her general health had been good.

Examination showed an elderly white woman acutely ill. Her temperature was 102, her pulse 100, her respiration was 26, her blood pressure was 106/54. Her face was flushed, her respiration was labored. Her weight was 130, her height 5 feet 2 inches.

Her eyes reacted to light and accommodation, her throat was congested. The heart was normal in size and free of murmurs. The pulmonic second sound was accentuated, the rate was rapid. Examination of the lungs showed dullness over the left lower lobe with increased fremitus and numerous moist rales. The right lung was resonant and free of rales.

The abdomen was tense and tympanitic. In the right lower quadrant, there was present a roundish elevated mass which was tympanitic and very tender. The patient was unable to relax the abdominal muscles.

The reflexes were present and equal. The uterus was small, senile, freely movable. The adnexa were not palpable.

The white blood count was 14,900 with 82% polys. The urine was within normal limits.

A diagnosis was made of Left Lower Lobar Pneumonia and Probable Intestinal Obstruction.

The patient was hospitalized. A flat plate of the abdomen was taken. There was no evidence of intestinal obstruction, nor was there evidence of a perforated abdominal viscus when the patient was later examined by the barium meal.

The patient was given sulfathiazole and general supportive treatment. She ran a typical pneumonia course. The house physician's progress note at the time of her discharge from the hospital reads, "The patient was brought to the hospital because of pain in the right lower quadrant of the abdomen and a questionable mass in this region. Under symptomatic treatment, it subsided and the symptoms cleared up. The pneumonia course was uneventful. The patient is discharged in good condition with normal pulse, temperature, and a symptomless abdomen."

Comment. Patient B. G. manifested an abdominal syndrome of pain, tympanitis, distention suggestive of intestinal obstruction as an expression of a lobar pneumonia. Of special interest is the contralateral relationship of the pneumonia to the location of the abdominal pain. The abdominal pain and the symptoms occurred on the right side while the pneumonia was on the left side. Pronounced meteorism which was quite evident in this case is a fairly common symptom in pneumonia. Kolmer (11) believes that its origin exists in the toxemia which is present in the disease. However distention which is sufficiently severe and sharply localized to suggest an intestinal obstruction is less common.

CASE IV. Lobar Pneumonia Simulating Gall Bladder Disease.

Mrs. M. M., a white woman of 52 years, was seen in her home. She complained of a dull nagging pain under the right costal margin of the abdomen which was about four days in duration. The pain was diffuse in character and involved much of the right upper quadrant of the abdomen, although it tended to localize in the gall bladder region. It radiated to the epigastrium and the right scapular region. At times the pain would become quite sharp, after which it would become dull again. She also complained of loss of appetite. If she ate a heavy meal, she became nauseated and would vomit. She felt bloated, belched considerably and was troubled with excessive flatulence. She was tired, fatigued easily, and felt warm. She had been told that she was having an attack of gall bladder colic.

Examination showed an acutely ill white woman lying on the right side with her knees flexed. She was slightly

cyanotic and dyspnoeic. She gave her weight as 125 pounds and her height as 5 feet 3 inches. Her temperature was 102, her pulse 96, her respiration was 28, her blood pressure was 96/50.

Her heart was normal in size, rapid, no murmurs were heard, the pulmonic second sound was accentuated. In the right lung there was present an area of dullness extending from the second to the fifth interspace associated with increased voice and tactile fremitus, also there was present numerous moist rales over the entire right lower lobe. The left lung was essentially normal.

In the abdomen, there was some spasticity of the muscles in the right upper quadrant where the patient indicated tenderness. The liver and spleen were not palpable. The reflexes were present and equal.

The blood count showed the R.B.C. to be 5,200,000; the W.B.C. to be 18,000, the hemoglobin to be 78%; and the differential to be, polys 85%, lymphs 14% and eosinophiles 1%.

The patient was hospitalized.

An x-ray examination of the chest (see photograph)



X-ray film of Mrs. M. M. showing a triangular area of almost homogeneous density in the lateral portion of the right second and third costal interspaces, apparently delineated by the interlobar fissure, indicating a pneumonic consolidation of the upper portion of the lower lobe. There is also present an infiltrative process in the median half of the right lower lobe suggestive of a pneumonitis of this portion of the right lower lobe.

showed a triangular area of almost homogeneous density in the lateral portion of the right second and third costal interspaces, apparently delineated by the interlobar fissure, indicating a pneumonic consolidation in the upper portion of the lower lobe. There was also present an infiltrative process in the median half of the right lower lobe suggestive of a pneumonitis of this portion of the right lower lobe.

X-ray examination of the gall bladder and gastrointestinal tract made at the request of the patient at a later period showed these organs to be essentially normal.

A diagnosis was made of Right Lower Lobar Pneumonia.

Subsequently the pulmonary consolidation spread to involve the entire right lower lobe. Sulfathiazole was given. Otherwise the treatment was symptomatic and supportive. No special attention was given to the digestive tract. The digestive symptoms subsided about the time of the crisis on the fifth day. Recovery was un-

eventful. The patient returned about six months later for observation and stated that she had been entirely free of her former gastrointestinal symptoms.

Comment. Patient M. M. manifested a syndrome of upper abdominal pain and other symptoms suggestive of gall bladder disease as an expression of a lobar pneumonia. The digestive distress was clearly functional in character and the abdominal pain was referred in origin. The digestive syndrome subsided when the pneumonia improved.

DISCUSSION

Pain originating in the pneumonic process of the lungs may be referred to the abdomen and thus simulate acute abdominal disorders, as acute appendicitis, gall bladder disease, gastric irritation, intestinal obstruction, as well as other abdominal crises.

In these patients, there may occur localized abdominal pain, nausea, vomiting, abdominal tenderness, tympanitis, localized rigidity, etc.

There is usually present certain associated constitutional symptoms, as high fever, rapid pulse, shallow respiration, leucocytosis, etc. These signs however are of little help in the differential diagnosis since they occur in both the abdominal crises and pulmonary disorders.

Pain is the commonest symptom which occurs in pneumonia; also it is the symptom of greatest frequency which occurs in disease in general. It is Nature's warning sign of danger. Usually it indicates an injury of some kind and directs attention to the particular region of the body in which the injury is located. As such, it is a helpful symptom; however at other times the pain may be referred to a remote organ or area. In these instances, the pain becomes a confusing manifestation of the disease which gives rise to it.

Although pain is a fairly constant expression of disease, nevertheless it is safe to state that its exact appearance is never the same twice. Its manifestations are infinite. It varies in its mode of onset, its duration, its required stimulus, its severity, its distribution, the time relationship to specific metabolic activities, its localizing power, its ability to incapacitate, its response to treatment, etc.; in fact it is so variable in its manifestations, that its interpretation often becomes a fine art. Other signs and symptoms are subject to measurement by instruments of precision; but pain remains a psychic phenomenon, conceived by the patient and interpreted by the physician according to their own limiting values. There is no yardstick for pain; pain considered both subjectively and objectively is a personal reaction, psychic in origin and valued by experience.

Abdominal pain in pneumonia bears little if any physiologic relationship to the pneumonia that gives rise to it.

Thoracic pain on the other hand, is to be expected, because the surface areas in which it occurs are supplied by nerves which come from the same spinal level that the inflamed lung tissue had its origin.

Normally the lung refers its pain to the surface area which is innervated by nerves which arise in the same spinal level in which the organ had its embryonic

origin. This seems to be the accepted explanation for the normal distribution of referred pain.

But abdominal pain has no embryonic segmental relationship to the lungs, hence its occurrence seems to be a physiologic paradox.

In a recent clinical study of abdominal pain arising in the lesions of pulmonary tuberculosis, we considered the toxic factor as a possible explanation to account for the production of the pain.

In pneumonia, we likewise consider the toxic factor as the probable explanation for the production of the pain. As in tuberculosis we observe that the toxemia of pneumonia consists of two factors, a specific toxemia elaborated by the pneumococcus and a non-specific toxemia resulting from the general fever process.

That a specific toxemia exists in pneumonia has been suggested by the work of Griffiths (12, 13), Dochez and Avery (14) and others. In 1891, Griffiths demonstrated in the urine of pneumonia patients a specific antigenic substance characteristic of the disease. In 1917, Dochez and Avery demonstrated that this soluble specifically reacting substance of pneumonic origin was present in the blood and urine of patients suffering with pneumonia, that it was considered to be toxic in character and that the presence of large amounts of it was considered to be an unfavorable prognostic sign.

The non-specific toxemia results from the general fever process, according to Macleod (15), Best and Taylor (16) and other writers. It produces certain chemical changes in the body. These changes result in an increased destruction of protein as indicated by the increase in the output of the uric acid, creatine, purine bodies, proteoses, albuminoses in the urine; also by the tendency towards a negative nitrogen balance; further there is a tendency towards acidosis. In the case of pneumonia, it has been specifically shown by Palmer (17) that there is excreted in the urine a large amount of organic acids. Further there is a tendency to a disturbance in the salt balance of the body in which an early salt retention is followed later by an excessive loss and demineralization.

Thus there appears to be ample proof that there exists a toxemia in pneumonia. This toxemia is made up of toxic substances which are soluble and which have been shown to be present in the circulation of the blood by Dochez and Avery. Being in general circulation, these soluble toxic substances are carried to all the viscera of the body including the digestive tract where some of them are absorbed.

As in the case of tuberculosis, we point out that a similar situation exists in this disease as a result of the presence of specific antigenic substance and non-specific toxic substances which circulate in the blood stream.

Further, it has been pointed out by Elwyn (18) that a similar situation exists in nephritis, where as a result of the failure of the kidneys to excrete the nitrogenous waste products, urea and other retention substances accumulate in the blood stream. The urea and some of the other substances diffuse into the digestive tract causing toxic symptoms.

If urea accumulating in the digestive tract produces severe gastrointestinal symptoms, and a tuberculin-like "protease" present in the active stage of tuberculosis is capable of setting up digestive disturbances, then it is reasonable to suppose that the soluble toxic substance elaborated by the pneumococcus which has been shown to be present in the blood stream may likewise initiate gastrointestinal symptoms as pain, nausea, vomiting, meteorism, flatulence, distention, constipation, etc.

The abdominal pain which occurs during the onset of pneumonia or during its course, we regard as a toxic expression of the pulmonary disease acting on the digestive tract.

Pottenger (19) however believes that there is present a visceral reflex to account for the production of the remote symptoms. He points out that the bronchi and lungs develop from a diverticulum arising in the upper part of the primary gut, hence have the same general innervation as the other parts of the enteral system. Ordinarily impulses from the lungs are transferred to the surface areas of the neck and chest supplied by the third to the fifth cervical nerves. However, it is possible for these impulses to be transferred through their intercalated neurons in the spinal cord to the digestive tract to give rise to the gastrointestinal symptoms.

There can be no question that it is theoretically possible to produce abdominal symptoms through the medium of the viscerovisceral reflexes; however, it must not be overlooked that the number of potential viscerovisceral reflexes is almost unlimited and an enthusiast could easily dispose of the whole subject of visceral symptomatology through the all too convenient medium of viscerogenic reflexes.

With a toxemia definitely shown to be present in pneumonia, we are inclined to consider the toxemia as the important factor in the production of the referred abdominal symptoms which occur at the onset or during the course of pneumonia.

SUMMARY

1. Thoracic pain occurs in eighty per cent of patients with pneumonia, while abdominal pain occurs in eight per cent of patients with this disease.

2. The occurrence of thoracic pain in pneumonia is a helpful symptom because it directs attention to the diseased organs, thereby aiding in their diagnosis; but the appearance of abdominal pain distracts attention from the disease giving rise to it, and so becomes a source of confusion.

3. Abdominal pain has little if any physiologic relationship to the pneumonia which produces it. It is a physiologic paradox.

4. Abdominal pain and other associated symptoms may be so pronounced as to completely mask the respiratory infection, and may simulate acute abdominal disorders, as acute appendicitis, acute cholecystitis, intestinal obstruction, etc.

5. The ability of referred abdominal pain and the associated symptoms to simulate acute appendicitis is annoyingly real at times; and laparotomies have been performed as a result of this mimicry.

6. The probable explanation for the production of referred abdominal pain lies in the toxemia which occurs in the disease.

7. The toxemia consists of two factors, a specific factor elaborated by the pneumococcus, and a non-specific factor resulting from the general fever process.

8. We regard the toxemia acting on the gastrointestinal tract as responsible for the production of the symptoms of abdominal pain, meteorism, flatulence, nausea, vomiting, distention, constipation, etc.

9. The differential diagnosis between the acute abdominal crises and pneumonia is arrived at by a painstaking consideration of all the available clinical material.

REFERENCES

1. Chatard, J. A.: Lobar Pneumonia in the Johns Hopkins Hospital, 1889-1905. Johns Hopkins Hospital Reports, 1910, 15, 55.
2. Brown, T. R.: Abdominal Pain: Its Significance and Diagnostic Value. Ann. Int. Med., 1934, 8, 343.
3. Norris, G. W.: Lobar Pneumonia. Osler's Modern Medicine, 1925, 1, 184.
4. Reiman, H. A.: The Pneumonias. W. B. Saunders Company, Philadelphia, 1938.
5. Gauss, Harry: The Interrelationship of Gastrointestinal and Renal Disease. Ann. Int. Med., 1936, 9, 1373.
6. Gauss, Harry: Gastrointestinal Symptoms of Pelvic Origin. Am. J. Dig. Dis., 1937, 3, 891.
7. Gauss, Harry: Gastrointestinal Symptoms from Cardiovascular Disease. Am. J. Dig. Dis., 1937, 4, 374.
8. Gauss, Harry: Gastrointestinal Symptoms in Anorectal Disease. Colorado Medicine, 1939, 36, 106.
9. Gauss, Harry: Gastrointestinal Symptoms in Disease of the Brain. J.A.M.A., 1939, 112, 501.
10. Gauss, Harry: Gastrointestinal Onset of Pulmonary Tuberculosis. Am. J. Dig. Dis., 1939, 6, 263.
11. Kolmer, J. A.: The General and Specific Treatment of Pneumonia. Texas State J. Med., 1938, 34, 460.
12. Griffiths, M. A. B.: Ptomaines extraites des urines dans quelque maladies infectieuses. Compt. Rend. Acad. Sc., 1891, 113, 506.
13. Griffiths, M. A. B.: Recherches sur les ptomaines dans quelques maladies infectieuses. Compt. Rend. Acad. Sc., 1892, 114, 506.
14. Dochez, A. R. and Avery, O. T.: Elaboration of specific soluble substances by pneumococcus during growth. J. Exper. Med., 1917, 26, 477.
15. Macleod's Physiology in Modern Medicine. C. V. Mosby Company, St. Louis, 1938.
16. Bert, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice. William Wood and Co., Baltimore, 1937.
17. Palmer, W. W.: Acidosis and Acid Excretion in Pneumonia. J. Exper. Med., 1917, 26, 495.
18. Elwyn, Herman: Some Present Day Concepts in Nephritis. Am. J. Med. Sc., 1930, 179, 149.
19. Pottenger, F. M.: Symptoms of Visceral Disease. C. V. Mosby Company, St. Louis, 1938.

The Physiologic Use of Water In Constipation

By

JAMES A. MCKENNEY, M.D.*

OAKLAND, CALIFORNIA

FROM the death of Galen, 201 A. D., to the appearance of Vesalius, there was no scientific progress in Medicine. Likewise we may add that the treatment of the most common digestive complaint, constipation, has adhered to medieval procedure more nearly than any affliction of the human race.

Constipation is only a symptom and, as usually considered, means the prolonged retention of the products of digestion within the intestinal canal by reason of infrequent or incomplete evacuations therefrom. It is a symptom that has been found in connection with practically every condition of the human body, both in health and with the multitude of diseased conditions which are encountered.

Rehfuss (1) says that nearly half of the entire population is so affected. Betha (2) says that 90% of people are constipated at one time or another. Bockus (3) says that obstinate constipation is one of the most frequent conditions which the physician is called upon to treat, yet there is probably no other disorder which is so often badly managed. Rehfuss (4) also states that constipation is often a symptom of a functional rather than any organic bowel defect.

The development, Anatomy and the Physiology of the Digestive tract are the necessary prerequisites, as Spencer (5) so aptly states, to a study of this condition.

Spiesmann (6) classifies constipation as:

1. Functional.

- (a) Disregard for habit time.
- (b) Sedentary habits and lack of proper exercise.
- (c) Insufficient water intake.
- (d) Deficiencies in diet, Bulk, Vitamins, Mineral salts, etc.
- (e) Instability of vegetative nervous system.
- (f) Endocrine.
- (g) Dyschesia (Rectal constipation).
- (h) Coprostasophobia.
- (i) Psychic and nervous factors.

2. Organic.

- (a) Kinks, Adhesion, Anomalies of the colon.
- (b) Gastroenteroptosis.
- (c) Prolapse, Rectum or Sigmoid.
- (d) Organic dyschesia.
- (e) Anal Pathology, pectenosis, cryptitis, and Anal stenosis.

Schwartz (21) divided Functional constipation into:

- 1. Ascending type, hypokinetic (Atonic colon).
- 2. Dyskinetic type (Spastic colon).
- 3. Dyschesia.

Bauer (7) says that Atonic and Spastic types of constipation are largely abandoned.

*Highland Clinic.

A study of this nature, naturally, could not include such conditions as acute appendicitis or other gross pathological conditions of the digestive tract or mechanical obstructions. It would be limited to those persons having a practically intact digestive system. In other words, we may well say "Essential Constipation."

Barker (8) says:—"Some cases of constipation appear to be due to an over utilization of the intestinal contents, with too good absorptive powers resulting in lessened fluid in the intestine, with insufficient chemical stimulus to the motility of the intestinal wall."

Maher (9) says:—"An excessive density of mucous protective film in the intestine prevents adequate irritation of the intestinal wall by the fecal mass." Rehfuss (10) says:—"It may be accepted as proved that water in the healthy adult is an active gastric stimulant and it would seem that water could best further the digestive plan when taken with meals." Cowgill and Anderson (11) state that "It is possible that the degree of hydration of the individual exerts some influence on laxation." Adolph (12) states "Water taken with other anabolic materials may be retained—that water taken with meals is alone destined to be a part of the body structure." Bergen (13) says:—"The importance of fluid intake in the management of constipation cannot be overemphasized." Bockus (14) says:—"An undue inspissation of feces and the development of constipation is encouraged by an insufficient intake of water." Rehfuss (15) says:—"An animal may lose all its glycogen and fat, one-half of its protein and still live, but if it lost one-tenth of its water, it died. Fatty infiltration of the liver results when animal is deprived of water." Spencer (5) says:—"Rapid reabsorption of water or deficient intake of water may produce a concentration and drying of the fecal mass to the extent that it becomes a poor stimulant of the defecation reflex."

The clinical dictum, that we must not drink water at meal time because this fluid dilutes the digestive juices and thus delays digestion, has been amply disproven by Hawk (16), Ivy (17), Neilson (18) and many others.

Not only does the water taken with meals stimulate the activities of the saliva, and the gastric juice, but there is ample evidence that digestion and absorption in the intestine are likewise favorably influenced. If water is taken between meals, there is the visual stimulus of gastric secretion but there is nothing to digest, therefore, in order to obviate the economic waste, the proper time for the normal person to drink water would seem to be at meal time. Rehfuss (15).

In this connection, it would seem proper to consider some of the properties of water in relation to its usefulness in the body as outlined by Barborka (19).

1. A Solvent.
2. Absorption of food.
3. Transportation of food.
4. Excretion of waste.
5. Keeps materials in tissues in solution, so that chemical reactions can take place.
6. Regulates Salt concentration.
7. Regulates body temperature.

The water supply of the body:

1. Water taken as such.
2. Foods with water content.
3. Oxidation water resulting from oxidation of the H. of Carbohydrate, Fats and Protein. A diet of 1/6 P., 1/3 F., 1/2 C., 100 Cal. yields 12 gm. oxidation water.

The water output of body:

1. Urine (varies).
2. Feces 60-120 gm.
3. Sweat—Resting body, 935 gm.
4. Expired air.
5. Sputum, Sperm, Menstrual fluid, Nasal secretion, Tears.

The blood being fairly constant in water content, 76-81%.

The process of digestion of food of all classes, Carbohydrate, Protein and Fat, is essentially a matter of hydrolysis, that is, water is added to the food and to that cleavage that is insoluble, water is again added, plus digestive juices, this process being repeated until all the digestible food is prepared for absorption. Then this water with its contained food is absorbed. So we have a mechanism whose work is to extract water from the inside of the bowel, this process leaving a more or less dehydrated residue within the bowel, this residue being a poor stimulus to the motility of the intestine results in its passage being further delayed, thus more complete dehydration, producing a dry hard mass in the lower bowel.

Some twenty years ago observations were begun in the clinics of 'The Oakland Health Center, later The Alameda County Institutions' Clinics, to determine the relationship of water to the symptom of constipation. In this study a record was made whether water was taken before, with or after meals; also the use of laxatives, etc.

It soon became apparent that those taking water with their meals did not require laxatives. Conversely those not taking water with their meals were users of various laxatives and cathartic medicines.

Constipation being, in most instances, a subjective symptom, requires skill and tact in questioning patients. For instance, after the usual inquiry regarding their appetite to ask if they are constipated—the reply will be "No," but to casually say "What do you take for your bowels?", will reveal the use of many usual, also many unusual, remedies for constipation. Somewhat similar methods must be employed at the patients subsequent visits to ascertain whether our instructions are being properly carried out. If this is not carefully

done, our data will be incorrect, consequently of no value.

Patients having constipation were instructed to discontinue the use of enemas, laxatives, cathartics, etc., and to take at least two or more glasses of water, either cold or hot, as preferred, along with their meals, regardless of other fluids taken such as tea, coffee, soups, etc. In obstinate cases, they were advised to take an additional glass of water some time before breakfast. In case there was no bowel movement for four or five days, they were to take a single S S enema—and this was not to be repeated. All patients were to report at the clinic at least once a week for questioning and observation.

477 patients were observed for varied periods of time. Ages 13 to 79 years. Male, 158, Female, 313, sex not stated, 6.

Patients with constipation, Male, 107, Female, 245.

82 patients were noted that did not have constipation and that did not take enemas, laxatives or cathartics of any kind, but they did take plenty of water with their meals. It is not difficult to conceive that possibly they were likely carrying over into the large bowel an excess of water over that actually required for the purposes of digestion of food and in this manner preventing dehydration of the food stream to a degree such as to produce constipation.

We find 352 patients who have constipation and take enemas, laxatives or cathartics, etc., and not taking water with their meals. Of this number no subsequent report could be obtained from 85 and 27 were un-cooperative in carrying out instructions. Of the remaining, 230 complying with instructions in discontinuing all forms of medication and after adopting the practice of taking water with their meals, all were found to be having regular daily bowel movements. Reports showed 72 as remaining well in this respect for periods of observation ranging from one to seven years. Of the patients in this group carrying out this line of treatment, no failures were observed, regardless of their other ailments.

Of the 27 patients classed as un-cooperative, seven were finally induced to comply with instructions and all seven became well in this respect. The remaining 20 patients continued to take enemas, laxatives or cathartics, etc., and were observed as a control group. All 20 remained in the same condition regarding their constipation.

Patients without constipation and taking enemas, laxatives or cathartics, etc., and taking water with their meals, 9 of these, 7 reported daily evacuations, after omitting medication, and 2 failed to report.

Patients with constipation and taking laxatives, etc., and taking water with meals, 7. Of these, 5 became well upon discontinuing medication, 2 failed to report.

Patients without constipation, not taking laxatives, etc., and not taking water with meals, 33; of this number 5 were subsequently reported with diarrhoea; 13 reported diets consisting largely of fruits and vegetables; 5 reported later as constipated and taking various remedies for that condition, and after discontinu-

ing medication and upon taking water with all meals, all became well in this respect.

The use of large quantities of fruits and vegetables is frequently effective as a remedy for constipation but in the final analysis, perhaps some of their effectiveness is due not only to their water content, but also to their ability to retain and carry water further along the digestive tract. The use of water before breakfast, also before and after meals, was noted, but after extended observation, the conclusion was reached that it was the water which was taken along with meals, that was most efficient in overcoming the symptom of constipation.

Of the total 477 patients, we find 345 taking water with their meals and not taking laxatives, cathartics, etc., and not having constipation. Of the 345 patients, we find that 256 were constipated and were taking

various remedies for that condition and became well upon the discontinuance of medication when they included a sufficient quantity of water with their meals.

This plan of treatment was not efficient unless all other forms of treatment or other medication was discontinued.

CONCLUSIONS

1. Persons not taking a sufficient quantity of water with their meals are generally users of laxatives, cathartics or other forms of medication taken for constipation.
2. The addition of two or more glasses of water to meals, being taken along with the food, generally obviates the necessity for the use of various remedies for constipation.

REFERENCES

1. Rehfuess, M. E.: M.N.N.A., 107:1298, 1939.
2. Betha, O. W.: J.A.M.A., 23:1268, 1936.
3. Bockus: *Gastro Enterology*, Vol. II, p. 521.
4. Rehfuess: *Indigestion* (Saunders Co.), p. 383.
5. Spencer: Am. J. Dig. Dis., March 1935, p. 7.
6. Spiesmann: Ill. M. J., 78:153, 1940.
7. Bauer, J.: Am. J. Dig. Dis., May 1940, p. 210.
8. Barker: Monographic Med., Vol. III, p. 403.
9. Maher: Med. J. & Record, Apr. 4, 1928.
10. Rehfuess: *Diseases of Stomach* (Saunders Co.), 1927, p. 961.
11. Cowgill & Anderson: J.A.M.A., Vol. 98, p. 1866-1871.
12. Adolph: J. Physiol., 1921.
13. Borgen: Wisc. M. J., 35:897, 1936.
14. Bockus: *Gastro Enterology*, Vol. II, p. 521.
15. Rehfuess: *Indigestion* (Saunders Co.), p. 404.
16. Hawk, Philip B.: *Endocrinology and Metabolism* (Lippincott), 1922, pgs. 280, 288 and 294.
17. Ivy, A. C.: Am. J. Physiol., Vol. 4, July 1, 1918, p. 420.
18. Nielson, C. H.: J.A.M.A., 64:1052.
19. Barboraka: *Tr. by Diet* (Lippincott, 1935), p. 20.
20. Borka: *Monographic Medicine* (Appletons), Vol. IV, p. 753-75.
21. Quoted: by Spiesman, Ill. Med. Jour., 78:153.

Vitamins and Hormones In Nutrition. II. Endocrine Dyscrasia

By

BENJAMIN F. SIEVE, M.D.

BOSTON, MASS.

IN an earlier publication (1) the synergistic action of vitamins and hormones was pointed out, and the influence on vitamin absorption of such contributing factors as hormone dyscrasia, infection, gastro-intestinal disease, reduced dietary intake, emotional upset, and trauma was discussed briefly. During the eighteen months since the preparation of the original communication, considerable attention has been focused on this problem, as a glance at the voluminous literature on the subject will prove. Moreover, the increasing incidence of deficiency cases, some perhaps caused by wartime food rationing, has made it evident that proper nutrition is an important war and post war problem, one which, as yet, has not been entirely solved by dietary measures nor by vitamin therapy. In view of this, it seems desirable at this time to follow the original communication which touched on these matters only generally, with a series of papers which will discuss in greater detail those factors which interfere with proper utilization of vitamins, and which may inhibit the synergistic action of vitamins and hormones in

their relation to nutritional deficiencies. Contributing factors, as presented in Chart I of the original publication, will be discussed individually in this series, and pertinent cases will be presented in illustration. An attempt will be made to present bizarre cases, as well as the more common types. The present communication, the second in the series, will be concerned with the influence of endocrine dyscrasias on nutrition.

Endocrine dyscrasia occurred in 96.5 per cent of the 200 cases presented in the original communication. From these figures it is evident that in any nutritional problem, after local and systemic disease have been ruled out, investigation should be made for glandular disorders which might produce hormonal imbalance. Here the physician is confronted with a difficult, sometimes bewildering, diagnostic problem, for it is frequently impossible to determine from clinical manifestations and findings alone the exact nature of the physiological disturbance. Dysfunction of the pituitary-ovarian-uterine mechanism in the female, or the pituitary-testicular-prostatic mechanism in the male, may be the underlying cause. On the other hand, these mechanisms may be upset by other functional abnor-

Junior Visiting Physician, Boston City Hospital. Instructor in Medicine, Tufts College Medical School.

malities, such as dysfunction of the hypothalamus, thyroid, adrenal, pancreas, or other glands of internal secretion. Such conditions as obesity, metabolic disorders, emotional and psychic disturbances may also contribute to the altered physiology. In these types of cases the underlying causes are usually multiple, and the symptoms do not group themselves into a clearcut textbook picture. Rarely, in fact, are distinct or full blown glandular deficiencies encountered in nutritional disturbances. Rather, it is the subclinical, early endocrine upsets that one sees.

Careful study, and detailed history, as emphasized in the original publication, and also in a more recent discussion (2), are essential to elicit the signs and symptoms of these subclinical glandular deficiencies. Analysis and correlation of all data is of paramount importance, because often apparently normal findings will, on investigation, yield the chief clue to the cause of the disorder. For example, the regular menstrual cycle, commonly accepted as an index to normal ovarian function, has been grossly misinterpreted and misunderstood. Hence it has been found not only misleading, but has often been overlooked as a key to diagnosis. A subjective history from the patient of normal catamenia is not adequate proof of a normal menstrual cycle, nor can regularity in the cycle or absence of discomfort, in themselves, be regarded as infallible criteria of normalcy. Detailed history may reveal diminished flow, irritability, depression, headache, insomnia, edema, polydipsia, carbohydrate intolerance, or mastodynia. Any one, or several, of these complaints may provide the clue to dysfunction of the ovarian, thyroid, or pituitary glands, or a combination of them.

The following case may help to clarify this point. A 23 year old, unmarried, white female complained of pernicious vomiting of four years' duration. Attacks occurred at monthly intervals, and lasted from three to twenty days. During the phase of vomiting the patient became dehydrated, irritable, depressed and weak, and lost 5-20 pounds. Periods of relief were so short that she could not regain her weight and strength before the next attack. In an effort to relieve her condition she had gone from one gastro-enterologist to another, and some fifteen gastro-intestinal series and Graham tests had been done over a four year period. Appendectomy and cholecystectomy had been advised. A neuropsychiatrist had labelled her condition neurosis, with cyclic vomiting. The patient was finally referred to the author for endocrine study.

When first seen this patient had been in an acute bout of vomiting for three days, and was still vomiting on the morning of the consultation. Because of her condition complete laboratory studies, including a basal metabolism test, were impossible. Careful blood studies were done, however, revealing a concentration of red blood cells, and a somewhat low hemoglobin. The urine was highly concentrated. Fasting blood sugar was critically low, as were the blood chlorides. Blood nonprotein nitrogen was slightly elevated. Basal metabolic tests, done ten days later, revealed moderately

low levels. This patient's menstrual history was apparently normal, a regular twenty-eight day cycle, five day flow, no dysmenorrhea. However, detailed questioning revealed that the present attack of vomiting had started two days after cessation of the last period, which had lasted only two days. On further inquiry the patient recalled that the previous month she had started to vomit three days before the period, this attack lasting nine days. Catamenia had started at age 17, and the first attack of vomiting occurred on the third day of her first period. The vomiting spells could then be traced to occur at any phase of the menstrual cycle, over the entire six year period. Thus, from a physiological point of view, they occurred at specific stages of the cycle: during the period of menstrual flow; immediately after cessation of flow, the phase of estrone production; eight to fourteen days after cessation of the flow, the phase of ovulation with corpus luteum production; or three to seven days before the onset of flow, the phase of corpus luteum hormone production and inhibition of the estrone production. However, correlation of data revealed that the most vomiting had occurred in the phase of maximum estrone production, thereby indicating a specific clue to therapy.

The patient was given 200,000 international units, 4 mg., of ketohydroxyestrone, intramuscularly, and within thirty minutes the vomiting stopped. Massive injections of estrone were given for six days, supplemented then by oral medication consisting of estrone, the whole vitamin B complex, and thyroid extract. A diet high in calories, minerals and vitamins was prescribed after the vomiting had been controlled. Parenteral therapy was continued, dosage averaging 600,000 units, 12 mg., of estrone per month, for twelve months. During this period, while receiving the injections, the patient was free from attacks of vomiting, although it was shown that attacks could be produced merely by omitting the injections for twenty to thirty days. The patient has had no vomiting spells for the past five years. She is now maintained on 3-4 mg. per month of Δ -estradiol dipropionate, parenterally administered, as well as on continued mouth medication. She has gained 25 pounds in weight, her appetite has improved, and her general health and nutritional status is good.

The three salient features in this case are first, the obvious effect of endocrine dyscrasia on nutrition; secondly, the necessity for detailed, analytical history in evaluating apparently normal findings; thirdly, proof that a history of normal catamenia can be grossly misleading if taken at face value.

The next case is one of typical endocrine dyscrasia, which started at puberty, and was supposedly corrected by surgery. But later, further endocrine imbalance followed, complicated by avitaminosis, which resulted in nutritional deficiency. A 23 year old, white, unmarried female complained of mastodynia, nervousness, insomnia, palpitation, loss in weight, and fatigue of two years' duration. These symptoms had been further aggravated by extreme emotional upset produced when

she had been told by a large clinic that bilateral mastectomy must be performed.

Catamenia began at age 11, and was apparently normal for three years. At 14 years of age the patient, in spite of a large appetite, began to lose weight, developed palpitation, sweats, tremors, dysphagia, and questionable exophthalmos. Varied therapeutic regimens had been prescribed for her over a two year period, including sedation, iodides, and x-ray therapy. None were effective. Her menstrual cycle became irregular, with diminished flow, dysmenorrhea, and finally amenorrhea of four months' duration. At age 16 a subtotal thyroidectomy had been performed, and for two months following this operation the patient did well, except for the fact that nervousness had persisted. Excessive palpitation and sweats disappeared. She gained 20 pounds in weight, and felt much stronger. Menstrual periods returned to normal. But this improvement had been only temporary, for after another four months, that is six months postoperatively, she had lost all of her weight gain, and most of the symptoms returned. The menstrual cycle again became irregular, with occasional amenorrhea, dysmenorrhea, and marked emotional instability for five days before onset. The patient had gone along in this condition for five years, at which time she observed small masses in both breasts. At the same clinic where the thyroidectomy had been performed, a small benign cyst was excised from each breast. Her age at this time was 21.

The patient was seen by the author in consultation two years following the cystectomy. During this period increasing cystic changes had occurred in both breasts, with increased nervousness and fatigue, and additional weight loss. Palpitation, tremors, and sweats returned. The picture was further complicated by peripheral edema, dyspnea, and vertigo. Catamenia became more irregular, lasting only one to two days, and was associated with severe dysmenorrhea, backache, insomnia, and occasional nausea and vomiting.

Physical examination revealed these positive findings indicating nutritional disturbance, vitamin and hormone deficiency. The patient was extremely thin, and the skin was somewhat dry. She had marked venous distention and a sense of fullness in both breasts, with cystic changes and thickening of Cooper's ducts. Nipples and areolae were normal. Bilateral cervical and axillary adenopathies were present. The abdomen was protuberant. There was some widening of the pelvis, and moderate accumulation of fat through the pretrochanteric regions. There was a fine tremor of the tongue, with atrophic papillae. Fine areas of leukoplakia were scattered throughout the buccal mucous membranes. Cardiac rate was rapid, with occasional extra-systoles. Diastolic blood pressure was high, with low pulse pressure. She had coarse tremor of the extended fingers and hyperactive reflexes. Laboratory findings were within normal limits. Basal metabolic rate was plus 8 per cent.

Upon analysis of this patient's history the rationale of the thyroid surgery appeared to be highly questionable. It had accomplished little, and had, moreover,

upset the ovarian and anterior pituitary gland function. As this glandular dysfunction became more pronounced, there was interference with vitamin absorption, because the synergistic action of vitamins and hormones had been disturbed. The emotional upset, produced when the patient was told that mastectomy was imperative, augmented even further the already existent disturbance in synergistic action of vitamins and hormones. Detailed history of the catamenia indicated impairment of all phases of the menstrual cycle. The normal pattern of production of estrone and corpus luteum hormone, as well as anterior pituitary hormones, had become completely upset. Herein lay the clue to therapy, complete hormone replacement, fortified by large doses of estrone which has been shown to be effective in cases of bilateral cystic mastitis (3).

Replacement therapy was administered parenterally three times per week, consisting of ovarian estrone and lutein hormones, anterior pituitary like hormone, and large doses of the whole vitamin B complex with ascorbic acid. Ketohydroxycortone, the whole vitamin B complex, and vitamins A, D, and C, were simultaneously administered by mouth. Within one month the cystic changes of the breast almost entirely cleared, with disappearance of the axillary glands, loss of tremors, sweats, palpitation, vertigo and edema. The periods became normal. The patient gained 10 pounds in weight. After three months of therapy the patient ventured the statement that she was "feeling fine." She had regained her highest weight level, extreme nervousness had subsided, and the breasts remained normal. At check-up examinations the basal metabolic rate was moderately decreased. She is now maintained on oral medication, as mentioned above, with the addition of small amounts of thyroid extract. Possibly within the next four to six months it may be necessary to give the patient another course of parenteral therapy.

The above case demonstrates the damage that can be done when the complete hormone balance is not considered. In this case failure to regard the entire endocrine picture resulted in hormone dyscrasia, vitamin deficiency, and indirectly, emotional or psychosomatic upset.

In contrast to the first two cases, the next is that of a male, aged 52, who complained of nervousness, fatigue, depression, and loss of weight. Reduction in weight was moderately severe, involving a loss of 15 pounds over a six month period. Nervousness, irritability, and depression had been present for ten years. Symptoms had become increasingly severe in the six months prior to consultation. The patient was particularly concerned over frequent crying spells, which occurred for no apparent reason. He also complained of flushes, palpitation, sweats, irritability, anorexia, insomnia, and reduced libido. Nocturia, frequency, and urgency had recently developed. Sedatives had been prescribed, but had caused only greater mental depression, and their somnific effect had diminished after only a few doses.

Physical examination revealed evident weight loss, dry skin, moderate peripheral arteriosclerosis, and

marked sclerosis of the retinal vessels. The heart was enlarged, and there was accentuation of the second aortic sound. Blood pressure was slightly elevated. The prostate gland was moderately enlarged and boggy. Dryness and loss of luster of the hair, extensive leukoplakia of the buccal mucous membranes, chronic blepharitis, cheilitis, atrophic papillae of the tongue, and pitted, ridged fingernails, all indicated subclinical avitaminosis. Fine tremor of the extended fingers was observed, and the reflexes were hyperactive. Laboratory data were essentially normal except for a low white cell count, and an increased relative lymphocytosis.

Here we have the classic symptom complex of the male climacteric (+), including nutritional disturbance. Onset of symptoms had occurred at age 42, but the patient went along fairly comfortably for a ten year period, at the end of which there was sudden exacerbation of symptoms and loss in weight, with moderate impotence. In the preceding cases it has been shown that the menstrual cycle in the female can indicate the clue to therapy. Analogous to this in the male is change in libido, or variations in degree of potency, as brought out by detailed history. This case was one of typical thyro-androgen deficiency, complicated by prostatitis. Infection, with the prostate as the focus, had upset the balance still further by interfering with the synergistic action of the hormones on vitamin absorption.

Treatment consisted of a high vitamin diet, supplemented by oral administration of an elixir of the whole vitamin B complex, vitamins A, D, C, and small amounts of thyroid. Androgen and estrogen were administered parenterally, and prostatic massages were given once per week. Symptoms cleared entirely after two months of treatment. Appetite returned, weight loss was entirely regained, and sleep restored, with complete alleviation of nocturia, frequency and urgency. Irritability, sweats, palpitation, and mental depression subsided, and libido returned to normal. For two years now the endocrine and vitamin balance has been maintained by oral medication, supplemented by occasional parenteral fortification, and prostatic examinations, including smears.

Attention should be called, at this point, to the fact that at the time of the original consultation with this patient, prostatic smears were entirely negative, as were the following two smears obtained at weekly intervals. However, negative smears in the presence of a boggy prostate gland do not indicate absence of infection. If parenteral substitution therapy with androgen and estrogen is given in conjunction with prostatic massages, later smears usually will be seen loaded with pus cells.

Early negative prostatic smears, after massage of enlarged prostate glands, have been the source of many errors in prostatic therapy. Many patients have been seen who have undergone a long course of prostatic massages by competent genito-urinary surgeons. They had been presumably cured, but when endocrine substitution therapy was administered in conjunction with the massages, prostatic smears were grossly positive for pus over a period of weeks or months. Micro-

scopic examination of the smears revealed large numbers of leukocytes, singly and in clusters. Many smears were sterile, but when organisms were found they were nonspecific and of mixed types. The foregoing case illustrates this pitfall in prostatic therapy. Parenteral substitution therapy with androgen and estrogen was administered along with the prostatic massages, and although the first three smears had been negative, the fourth prostatic massage produced smears which were loaded with pus. This continued so for twenty consecutive weeks.

In the original communication the effect of the female menopause syndrome on vitamin absorption was discussed. This syndrome is perhaps the most common type of endocrine dyscrasia that comes to the attention of the practitioner. Because of its frequent occurrence, and because of its influence on vitamin absorption and nutrition, the presentation of at least one case illustrating this syndrome in greater detail seems to be warranted.

A 48 year old, white widow complained of fatigue, weakness, palpitation, insomnia, headache, anorexia, constipation, nervousness, depression, and weight loss of eight years' duration. A diagnosis of "mild anemia" had been made, for which had been prescribed iron pills of several types, and during the three years preceding the present consultation she had received intramuscular injections of iron. A variety of sedatives had also been administered, but they seemed only to depress her further. During the six months prior to consultation symptoms had become aggravated, with severe flushes, myalgias, and arthralgias. Graying of the hair, which had been very slight at first, now advanced markedly, with considerable loss of the hair as well. The patient complained of paresthesias of the upper and lower extremities, coldness, dryness of the skin and hair, and brittleness of the fingernails. The menstrual cycle had been normal until twelve years before, when, because of metrorrhagia, the patient had received a course of x-ray treatment, following which the periods became infrequent and scanty, and were preceded by hyper-irritability, crying spells, and migrainous headaches. Eight years later, on cessation of the flow, there was marked vulval pruritus. The patient had lost 6 pounds during the six months directly preceding the present consultation.

Physical examination revealed the following. The patient was extremely thin, the hair was scanty and dry, the tongue smooth, with marked atrophic changes in the papillae. Mucous membranes were pale and dry, and numerous fine leukoplakial areas were scattered throughout the buccal mucous membranes. The heart was small, the sounds of poor quality, with bradycardia, and marked accentuation of the first mitral sound. Blood pressure was low, with a low pulse pressure. Considerable distention of the abdomen was observed. The rounded, smooth edge of the liver was palpable just below the right costal margin. Pelvic examination revealed typical atrophic changes, glistening mucous membranes, and moderate erosion of the cervix with a few superficial ulcers. Uterus and adnexa

were of senile type. There were moderate hypertrophic changes in the larger joints, and Heberden's nodes of the fingers. The skin was dry, with some loss of elasticity, and there were several small pigmented and telangiectatic nevi. Extremities were cold. Pulsations of the dorsalis pedis vessels were barely palpable. Fingernails were extremely brittle. Coarse tremor of the extended fingers was observed, and the reflexes were hyperactive.

Laboratory data showed only slight variation from the normal. Basal metabolic rate was minus 14 per cent. Urine was of low specific gravity, with moderately alkaline reaction, pH 6.0. Microscopic examination of the sediment revealed a few crystals and pus cells. Hemoglobin was 84 per cent, red cell count 3,860,000, white cell count 6,750. Differential smear was normal. Fasting blood sugar was 112 mg. per 100 cc., fasting blood nonprotein nitrogen 33 mg. per 100 cc. Electrocardiogram showed prolonged PR and QRS intervals, low voltage throughout, and inversion of T₂.

The patient was placed on a high caloric, high vitamin diet. Estrone, thyroid extract, capsules containing vitamins A, C, D, para-aminobenzoic acid, and a liquid vitamin B complex of high potency, were administered orally. Parenteral therapy was given three times per week, consisting of estrone, anterior pituitary like hormone, crude liver, thiamine chloride, and vitamin B complex. Relatively small dosage of estrone was employed, only 10,000 international units, 0.2 mg., of ketohydroxyestrone being given twice per week. The reason for this conservative dosage was the fact that the patient had previously received a course of x-ray therapy over the uterus. In such cases the author has observed that vaginal staining will frequently follow large intramuscular doses of estrone.

The patient continued on this regimen of oral and parenteral therapy for three months. Monthly check-up examinations were made, including complete laboratory data. Marked improvement in all symptoms was observed at the end of three months, with a gain in weight of 8 pounds. Laboratory data at this time revealed a basal metabolic rate of plus 1 per cent; red cell count 4,490,000; white cell count 7,950; hemoglobin 90 per cent. Fasting blood sugar was 100 mg. per 100 cc.; fasting blood nonprotein nitrogen, 28 mg. per 100 cc.

In this case it is noteworthy that, although iron had previously been administered both orally and parenterally without success, the blood counts and hemoglobin were restored to normal levels with the substitution therapy described above. Similar improvement in blood counts has been effected in many other cases which had previously failed to respond to long courses of iron therapy. Particularly has this been noted at the time of the climacteric in both the male and female.

The patient under discussion has been maintained symptom free, and at normal weight level for the past five years with oral substitution therapy in conjunction with parenteral therapy once or twice per week. The role of parenteral liver therapy in the regimen is

to act as a detoxicant on the liver, so that hormones taken orally can be properly assimilated, thereby aiding vitamin absorption. Again it must be emphasized that everything possible should be done to restore all structures and organs to as nearly normal a physiological condition as possible. The sooner this is attained the more efficiently do substitution hormones act, and thus the more readily and completely, by synergistic action, are the given vitamins absorbed and utilized by the body as a whole.

Another misconception which has frequently proved misleading in medical practice concerns the duration of the menopause syndrome in both the female and the male. Many physicians consider the cessation of the menses to be synonymous with termination of the menopause in the female. This, however, is an erroneous assumption, as the end of the menstrual phase marks only the termination of the reproductive period, but most emphatically does not indicate termination of ovarian hormone function. Although at the period of the male and the female climacteric, the testes in the male, and the ovaries in the female atrophy and decrease their hormone production, the anterior pituitary gland, the adrenal gland, and to some degree the thyroid gland, all continue to help in the maintenance of hormonal balance. From the clinical point of view, symptoms identical with those of the climacteric syndrome may be encountered in the postclimacteric period, and interference with the synergistic action of vitamins and hormones is sometimes even more marked. Despite the general practice to omit treatment following the supposed subsidence of the climacteric syndrome, substitution therapy has proved of tremendous benefit in this postmenopausal group. The following cases of a male and female at the sixth decade of life, well beyond the climacteric age, may serve to demonstrate this point.

A 60 year old, unmarried, male, complained of irritability, fatigue, depression, loss of weight, insomnia, palpitation, slight constipation, nocturia, and hypertension of ten years' duration, and occipital and vertex pressure of five months' duration. Ten years previously the patient had developed a prostatic syndrome for which he was treated by transurethral dilatation. Symptoms subsided temporarily, but shortly recurred, and persisted to the present time, with increasing nocturia, dribbling, drawing pain in the legs, and a decreased calibre of the stream. Six months prior to consultation a diagnosis of coronary thrombosis had been made. For the past five years the patient had suffered from recurrent attacks of left trigeminal neuralgia, which had caused extreme discomfort. Relief from this had been obtained only by absolute alcohol nerve injections at two or three month intervals. Reduction in libido had been observed during the last ten years, becoming more pronounced during the last two years.

At examination the physical findings were typical of the postclimacteric group. The hair was dry and lusterless, with some frontal recession, and slight achromotrichia. Leukoplakial areas were scattered throughout the buccal mucous membranes, and slight recession

and softening of the gums was observed. There was two plus edema of the upper and lower eyelids, with redness of the contact edges. Fundal examination revealed marked narrowing of the vessels, moderate arteriovenous nicking, and yellow pigmentation along the borders of the larger vessels. The tongue was slightly coated, with atrophic changes at the tip and lateral borders. The thyroid was somewhat enlarged. A few cervical adenopathies were observed. The heart was moderately enlarged, sounds were of good quality, with slight accentuation and roughening of the first mitral sound. Grade 3 systolic mitral murmur was heard, and the second aortic sound was greater than the second pulmonic. Blood pressure was 194/108. The prostate was moderately enlarged and boggy. The skin was thickened and dry throughout, with numerous pigmented nevi and an occasional telangiectatic nevus. Extremities were cold, dorsalis pedis was barely palpable, and fingernails were flattened and ridged. Slight hypertrophic changes were observed in the larger joints. Reflexes were normal, except for diminished knee and ankle reflexes. Laboratory findings were within normal limits. The basal metabolic rate was minus 3 per cent, and the fasting blood nonprotein nitrogen was 38 mg. per 100 cc.

The patient was placed on a regimen of oral and parenteral substitution therapy. An elixir of the B complex, riboflavin, small amounts of thyroid, and a synthetic estrogen which simulates the action of the natural estrogens, were all administered orally. Injections were given twice a week, consisting of the male hormone, the dipropionate radical of estrone, liver, ketohydroxyestrone, thiamine chloride, and the whole B complex with vitamin C, the last being given intravenously. In addition the patient received weekly prostatic massages.

At a check-up examination one month later the patient's general condition showed definite improvement, with disappearance of many of the subjective symptoms. General symptoms such as irritability, fatigue, and insomnia had entirely disappeared. Occipital and vertex pressure was greatly relieved, and prostatic symptoms had subsided. Libido was markedly improved. At examination improvement was found in all physical findings, with reduction of the blood pressure, and heart measurements nearly within normal limits. The prostate was much smaller, with only slight boggy remaining. Basal metabolic rate was plus or minus 0 per cent, and fasting blood nonprotein nitrogen 32 mg. per 100 cc.

This patient has been maintained symptom free for over a year on a regimen of oral and parenteral substitution therapy similar to that described above, in addition to weekly prostatic massages. His condition has continued to show improvement, with complete subsidence of all general complaints. His appetite has improved, and there has been an appreciable gain in weight. A complete change in personality occurred, with loss of the depression, irritability and lassitude. Improvement in libido and potency was pronounced. The left trigeminal neuralgia has not recurred. This

clearing of the neuralgia is attributed to two factors: first, eradication of the prostatic infection; and secondly, administration of biweekly injections of thiamine chloride in dosage of 200 mg.-300 mg. per injection. No alcohol injections have been required in more than fifteen months.

In contrast to the preceding case, the next is that of a 60 year old, unmarried female executive whose chief complaints involved a multiplicity of symptoms associated with hypertension, chronic cholecystitis, bronchial cough, and deafness, over a period of twenty-five years. Allergic manifestations such as sneezing, food sensitivity, and wheezing had been present for fifteen years. Although the catamenia had completely stopped at age 40, the patient had continued to complain of irritability, flushes, depression, insomnia, and loss of weight. In the six months prior to consultation, frequent attacks of palpitation and paroxysmal auricular fibrillation had occurred. During the same period there had been a loss of 10 pounds in weight, accompanied by marked anorexia.

Physical examination revealed findings consistent with hypertension and chronic cholecystitis with cholangitis. The skin and hair were dry, the nails brittle. Marked atrophic changes were observed on the tongue, and numerous leukoplakial areas were noted throughout the buccal mucous membranes. Both lung bases were filled with coarse crepitant rales. The abdomen was distended, the liver palpable and tender. Moderate hypertrophic changes were present in all the larger joints and fingers. Peripheral reflexes were hyperactive. Laboratory data gave evidence of mild hypochromic anemia. Fasting blood sugar was low. Basal metabolic rate was plus 12 per cent.

Therapy was somewhat more difficult in this case because of the patient's allergic history. Substitution therapy consisting of ketohydroxyestrone, thyroid, and the whole B complex, was given orally. Δ -Estradiol, ketohydroxyestrone, and thiamine chloride were administered parenterally, once or twice per week. After the patient had been desensitized, injections of liver extract were also given once a week.

After three months of therapy the patient showed marked improvement in her nervous symptoms, flushes, and palpitation. Blood pressure was moderately reduced. The appetite increased sharply, with a resultant gain of 8 pounds in weight. In addition to the substitution therapy, duodenal drainage was done at monthly intervals, resulting in marked improvement, after four months, in the cholecystitis and cholangitis. At this time decholic acid was given orally each day.

Parenteral therapy has been continued, at intervals, over the past five years, along with oral medication. The patient has been maintained at a comfortable level, with only rare untoward symptoms. Particularly noteworthy is the fact that there has been no recurrent episode of paroxysmal fibrillation throughout this five year period. With restoration and maintenance of the vitamin hormone balance the weight has returned to a normal level, and the body nutrition has been excellent. The hypochromic anemia completely cleared,

and the fasting blood sugar remained at normal levels. The basal metabolic rate has been within normal range, the last reading being plus 2 per cent.

These last two cases, representative of the postclimacteric group in the male and female, demonstrate that the age factor, in itself, is of little significance as regards the balance of the sex hormones and vitamins. Many cases have been seen, even in the seventh and eighth decades, with this same symptom complex, in which a definite imbalance has been found.

From a series of 200 cases selected for observation, 6 representative cases have been reported in detail. In these 6 cases, as well as in 96.5 per cent of the total series, there has been one constant factor, endocrine dyscrasia with attendant vitamin deficiency. Other details have varied, age groups have differed, extreme variation in history and symptomatology has been encountered, but the one constant and fundamental finding has been endocrine dyscrasia which has upset the vitamin hormone balance and interfered with their synergistic action, resulting in nutritional deficiency. In each case previous therapy had brought but little, and only temporary relief, but with adequate and continued substitution therapy the vitamin hormone balance has been restored and maintained at proper levels. Alleviation, and in many cases complete disappearance of symptoms ensued, and a good nutritional status was maintained.

In view of the severe post war problems in nutrition with which all practitioners will be confronted, not only at home but in occupied countries as well, this problem of endocrine and vitamin balance seems worthy of serious consideration. It might well become a portion of the protocol in a world food and nutrition conference.

SUMMARY

1. The effect of endocrine dyscrasia on vitamin absorption, and the resultant interference in the synergistic action of vitamins and hormones has been demonstrated.
2. Six representative cases, selected from a series of 200, have been discussed in detail.
3. Alleviation of symptoms, and pronounced improvement in general nutritional status was effected by substitution therapy.
4. In cases of the type herein presented, the underlying disorder is almost invariably obscure, but detailed history, careful analysis, and correlation of all data will provide the clue to diagnosis and frequently reveal the key to proper therapy.
5. Substitution therapy must be administered from the point of view of the entire endocrine picture, and should provide complete hormone replacement.

REFERENCES

1. Sieve, B. F.: Vitamins and hormones in nutrition. *Am. J. Dig. Dis.*, 11:179-181, June 1944.
2. Sieve, B. F.: Discussion. Allen, F. N., Clinical management of weakness and fatigue. *J.A.M.A.*, 127:960, April 14, 1945.
3. Bucher, N. L. R. and Geschlichter, C. F.: Pregnanediol and estrogen output in the urine of patients with chronic cystic mastitis. *J. Clin. Endocrinology*, 1:58, 1941.
4. Sieve, B. F.: Discussion. Werner, A. A., The male climacteric. Report of fifty-four cases. *J.A.M.A.*, 127:710, March 24, 1945.

Redundancy of the Colon

By

ARNOLD GALAMBOS, M.D.

and

WILHELMINA MITTELMANN GALAMBOS, M.D.

NEW YORK CITY, NEW YORK

REDUNDANCY of the colon indicates a disparity between the length of this organ and that of the body. In Kantor's definition "the redundant colon is one which is too long to fit into the body of its owner without undergoing reduplication." Redundancy refers exclusively to the length of this organ, while the width and circumference remain unchanged. In contradistinction to this, megacolon affects the width of the colon, leaving the length of the gut unchanged. Of course, transitions may exist between the two, and likewise they may both be present simultaneously. In either case the capacity of the colon is considerably increased—more so in megacolon. Kantor observed the amount of the enema fluid required to fill the colon fully, increased from the normal average of 38 to 46-120 ounces in redundancy, and according to White 3, or 4, or even more quarts of enema fluids were required to produce this effect. In megacolon the increase in capacity amounts to several hundred percent, even reaching as high as a ten-fold figure.

There are exact measurements at our disposal concerning the total length of the colon both under normal conditions and in redundancy. Naturally, such measurements were made in the cadaver, and even the most accurate x-ray films can not offer more than an approximate idea as to the exact measurements in vivo. According to Bryant, Curschmann, etc., the average colon measures about 1.5 meters (5 ft. and 2 in.) and the physiological variations range from 1.25 to 2 meters. In Curschmann's observation the greatest length of the redundant colon, even in extreme cases, did not exceed the length of 2.8 meters. Assuming an unchanged tonus and width of the colon in redundancy, the maximal additions to the length should not represent more than 40-50%. In an average case of redundancy there may be only an increase of 10-25%. Both of these figures are well in line with estimations based on appraisals of the x-ray configurations of colons. Accordingly the maximal capacity of the colon in redundancy, representing an increase of several hundred percent above the normal, as claimed by Kantor, White, among others, seems to be rather excessive, if not incomprehensible. In our own observations the amount of the barium enema required for the total filling of the colon in redundancy was not, as a rule, excessively high.

HISTORICAL

Modern clinical knowledge concerning redundancy of the colon is intimately connected with the advent of the roentgen era. Prior to this period no proper clinical or surgical appraisal of such conditions was even

conceivable. This well defined developmental abnormality is of frequent occurrence, and it is characterized by well known distinctive features. Its effect and its potential danger upon its carrier is fairly uniform and readily explainable. For these reasons its classification into a group by itself, as an entity sui generis, as advocated by Kantor, White, Larimore, etc., seems to us well warranted.

The literature on this topic is exceedingly meager. There are hardly a handful of publications on this topic and some modern and large textbooks, even of recent date, fail to describe or even mention this pathological condition. Others bring only cursory remarks or devote insufficient space, incommensurate with its significance in Medicine.

During the pre-roentgen era descriptive anatomy dealt with the problem of morphology of the colon, including observations and measurements of the length and configuration, and also dealt with its relation to the ligaments, bands, membranes and the mesentery. Curschmann is being credited with having tried to overcome the hiatus existing between the observations of the anatomist and the clinician. He made post mortem studies, measurements on the colon, and attempted a systematic study of the possible relation between these malformations and various clinical manifestations. Describing the various "Verschlingungen und Verbiegungen der Gedaerme", he characterized them as "die grotesksten, fuer den Operateur kaum, fuer den Anatomen nur schwer zu entzaetselndn Situs-bilder."

Harvey's survey gives an excellent account of the historical background and developmental study of the colon in general, and that of the redundant colon in particular. He was also concerned with its relation to the mesentery, omentum, membranes and ligaments in the abdomen, from early embryological life to adult age. Hundreds of years ago anatomists made studies and contributed to this topic. Mentioning, among many others, the contributions made by Mueller, Huschka, Rokitansky, Virchow, Engel, etc., he appraises the effect of an excessive or deficient migration, rotation, descent and fixation of the colon, as playing a predominant part in the developmental abnormalities, among which redundancy is one of paramount importance.

J. Bryant makes reference to the fact that the colon reaches practically its full length, that of an adult's, at the early age of ten, thereafter the growth affects only the width of the gut. However "the colon continues to grow throughout with advancing age actually

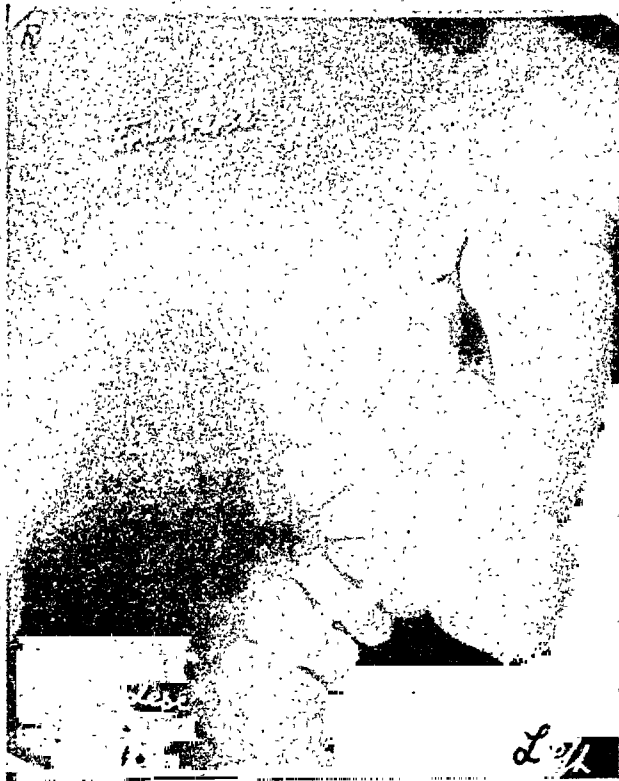


Fig. 1 (case I) — Severe redundancy of the splenic flexure. Barium enema.

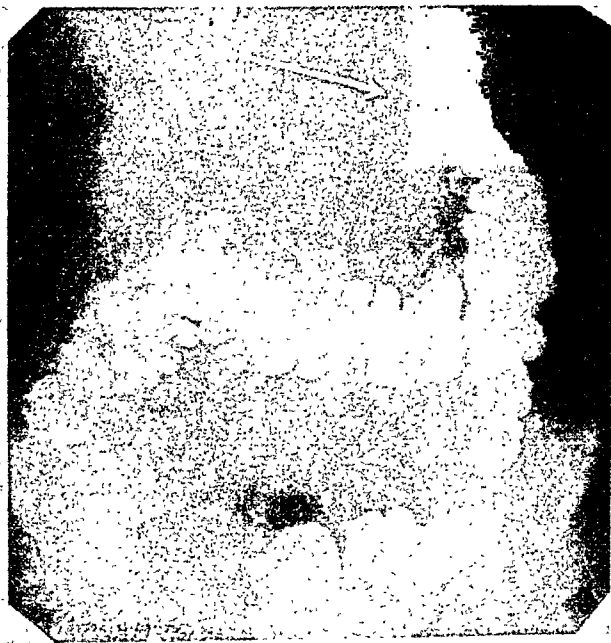


Fig. 2 (case I) — Splenic flexure apparently perfectly free of redundancy, proving normal functional power of the colon. Barium meal.

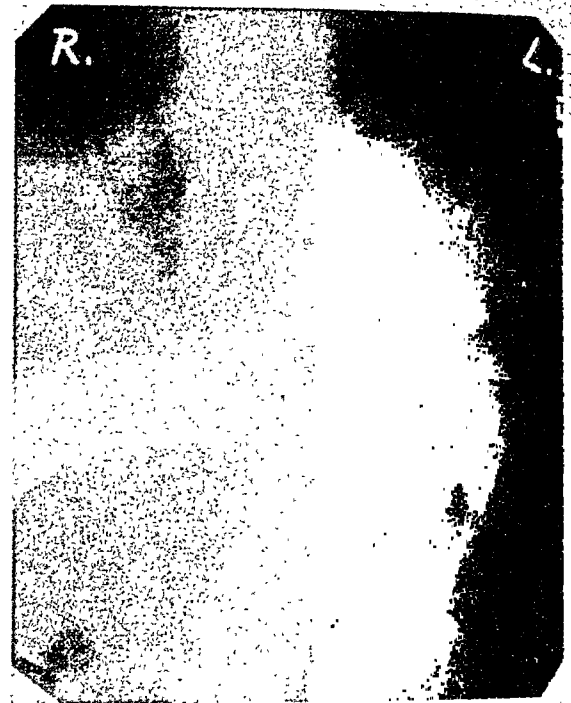


Fig. 3 (case II) — Redundancy of the splenic flexure. Barium enema.

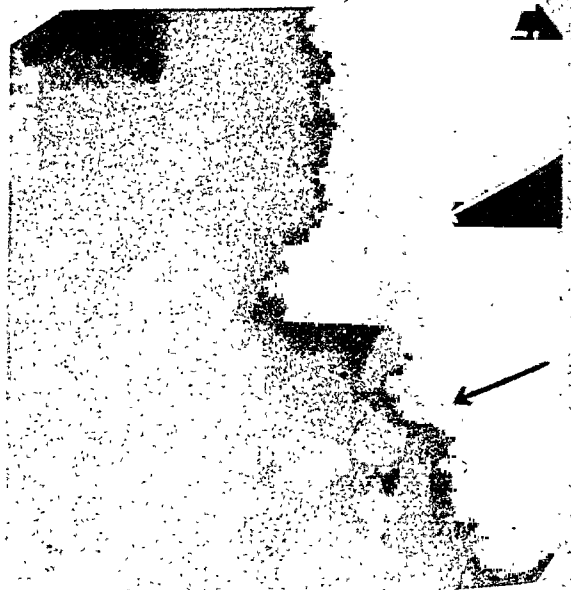


Fig. 4 (case II) — On progress meal gas and some barium retention is noted over some of the redundant loops, suggestive of impaired motor power. Clinically: pain, gas-distress, abdominal suffering, for the last 4 years. 42, male, plethoric.

and in relation to the small intestine" . . . and thus, the tendency to redundancy must increase with age — an implication that the size of an adult's colon is changeable and that it is generally longer in old age than that of the average adult's. Bryant quotes Spigelius who in 1632 found a definite ratio between the

body height and the total intestinal length, expressing it as 1:6.

Recent observations, contributions, and studies seem to favor the teaching of Treves, who challenges the old notion that "anatomy is a worked-out science", as being erroneous in general and emphasizes the fallacies of such teaching particularly in relation to the colon.

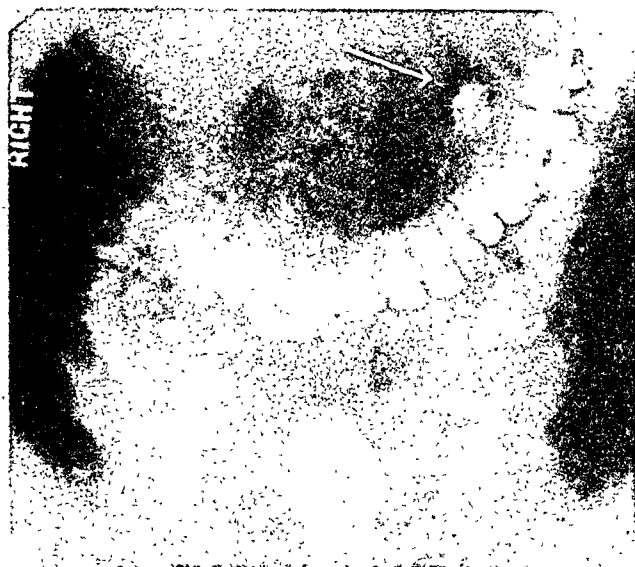


Fig. 5 (case II) — Barium in a "knuckle", enveloped by huge gas masses, without visible connection with the rest of the colon, or with the redundant splenic flexure. (Gas accumulation always seen on scout films.)



Fig. 6 (case III) — Redundancy of maximal degree of the hepatic flexure, with tremendous gas accumulation in the convoluted loops. Less conspicuous gas amounts along the aboral half of the colon. Sigmoiditis, diverticular state (rectoscopy). Barium enema. Male, 61, average build; suffered about 36 hours ago agonizing pain during a volvulus-like severe attack, which cleared up without surgery.

INCIDENCE

Redundancy of the colon is a very common anomaly. In 1924 Kantor diagnosed 62 cases out of a total of 668, representing an incidence of 9.5%. In 1931 he reported about 1614 observations with an occurrence of redundancy in 258 cases, a 16% incidence. This



Fig. 7 (case III) — Partial evacuation. Huge gas accumulation, mostly in the hepatic flexure, some gas elsewhere in the colon including the sigmoid loops. Hyperdescent of the cecum, with cecum mobile of maximal proportion. Appendix located centrally, at the center of the sacral vertebra.

difference in frequency as observed by the same author within a few years' range seems to us very significant, inasmuch as it serves to indicate that careful search, intense effort and special experience may increase the percentage of the recognition of certain diseases or states, in which the extra-work and the extra-time element involved seems to be prohibitive to the average worker or to the rushed man. F. Moeller found redundant colon 18 times out of a series of 744 cases of gastro-intestinal import. This represents 2.4%. He tried to explain the discrepancy in incidence by the fact that Kantor might not have been as critical as he was in selecting his material. White mentions that among 2,000 consecutive cases of gastro-intestinal import he found redundancy in severe form in 1-1/3 percent, together with about twice as many milder forms, making a total of 4%. Larimore, among 562 cases, encountered redundancy of the colon with a seat in the sigmoid in 18%, and in all other localizations in an additional 7.5%. He also subjected 116 newborn infants to barium enema study and found redundancy with other developmental anomalies in the infant, with at least the same frequency and variation as encountered in adults.

In the cadaver Bryant found a 14% incidence among 242 subjects, and Curschmann noted elongated sigmoid 15 times among 233 cases of post mortem material. In his study, the average colon measured 142 cm., with 195-280 cm. in the redundant colon. The



Fig. 8 (case IV) — Redundancy of the colon, affecting nearly all the segments (sigmoid, descending, transverse colon; hyperdescent of cecum). Male, 35, underweight, highly neurotic. No suggestive signs or symptoms of redundancy, inconclusive G. I. complaints. No constipation. Considered as having "nervous stomach", also "food allergy".



Fig. 10 (case VI) — Redundancy of the descending colon. Obscure clinical picture. Low backaches and epigastric pain. No constipation. Female, 28, average build. Past appendectomy and cholecystectomy.



Fig. 9 (case V) — Redundancy of the descending colon. Female, 37, average build. Anacidity, hunger pain, constipation. Past appendectomy.

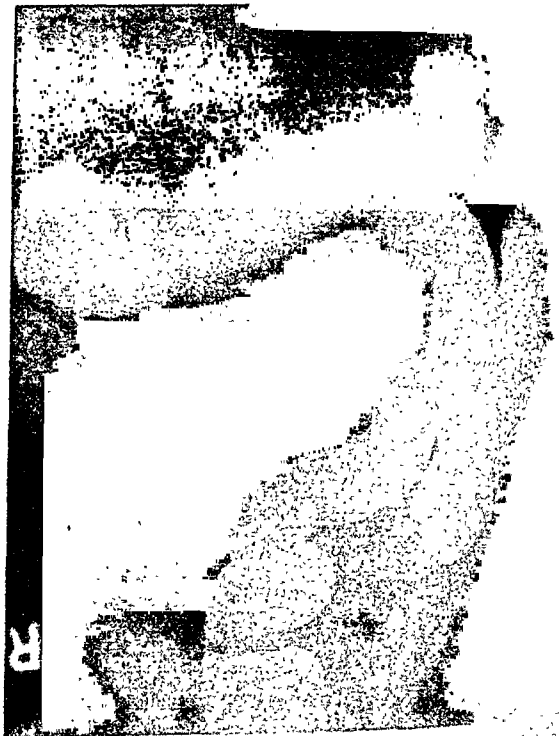


Fig. 11 (case VII) — Redundancy of the descending colon. On repeated examinations the redundancy of the distal colon appeared in an ever changing shape and configuration. No constipation. Obstinate heartburns, for 4 months, without any other G. I. complaints. Male, 63, obese.



Fig. 12 (case VIII) — Redundancy of the sigmoid, describing a double circle, and that of the splenic flexure. Constipation and other G. I. complaints for 4 months only. Female, 64, average build. Past cholecystectomy.

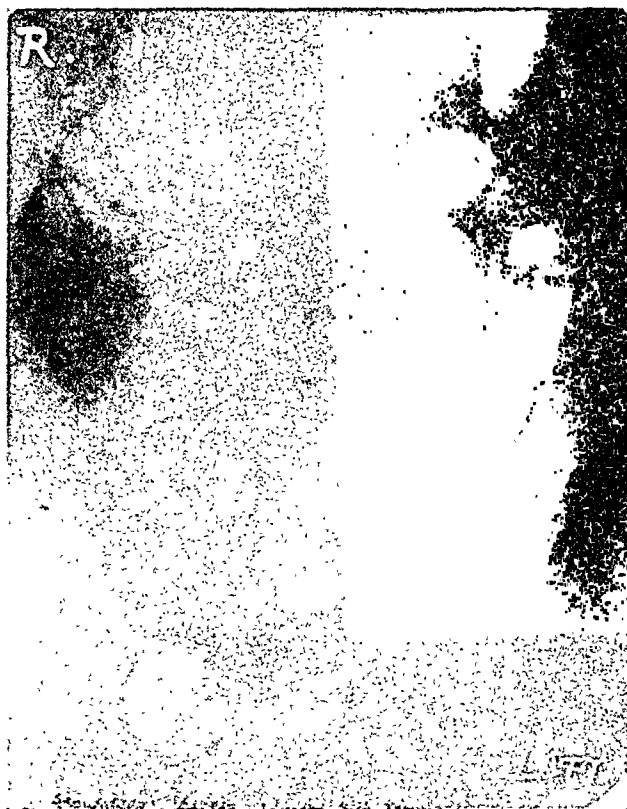


Fig. 14 (case X) — Redundancy of the descending colon. Note the location of the redundant segment, left to the colon. Barium enema.



Fig. 13 (case IX) — Redundancy and migration of the descending and sigmoid colon to the right, reaching beyond the cecal region. Loose bowels, mild colitis. Male, 44, plethoric. Past rectal operations, twice.



Fig. 15 (case X) — Barium enema at some other date shows a grotesque, double S shaped sigmoid, migrated to the right; the descending colon, now, remaining unaffected. Male, 41, stocky, obese. Suffered from mild ulcerative colitis. Two years later succumbed to cancer in the redundant loop.



Fig. 16 (case XI) — Huge redundancy of the hepatic flexure. Scout films show gas accumulation. Impaired motility. Intermittent, severe attacks, indicative of chronic obstruction, close to the proximal portion of the transverse colon. For last year "gas-attacks" daily, in previous years rarer. Male, 50, normal build. Past appendectomy, 4 months ago; cholecystectomy 8 years ago. Treated for peptic ulcer. In addition to redundancy, postoperative adhesion may be a contributory factor.



Fig. 18 (case XII) — Twenty-four hours film. Redundancy of the descending colon more pronounced. Barium given orally, in both cases.

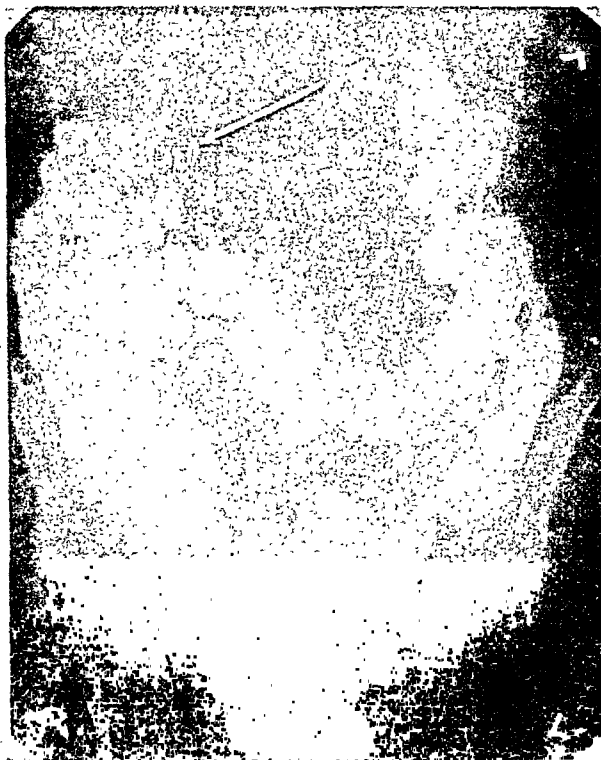


Fig. 17 (case XII) — Redundancy of both, the hepatic flexure and the descending colon. Six hours film. Redundancy of the hepatic

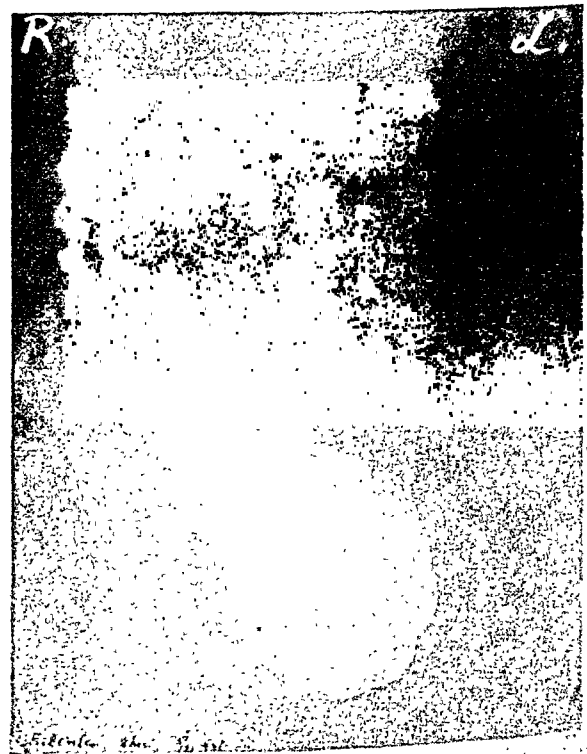


Fig. 19 (case XIII) — Hyperdescent of the cecum. Female, strongly built, 36. No constipation. Recent gastric resection for pyloric stenosis, due to ulcer. Appendectomy one, cholecystectomy six years back.



Fig. 20 (case XIV) — Maximal hyperdescent of the cecum with a superadded, unusually high hepatic flexure, producing an enormous elongation of the proximal colon. It is abnormally elongated and "retched", as against being elongated and curled, as in customary redundancy. Nevertheless it is redundant, inasmuch as it is too long for its owner. Male, 19, stocky, strongly built: unusual attacks of indigestion, with diarrhea and pain, for 2 years. past jaundice for 1 year.

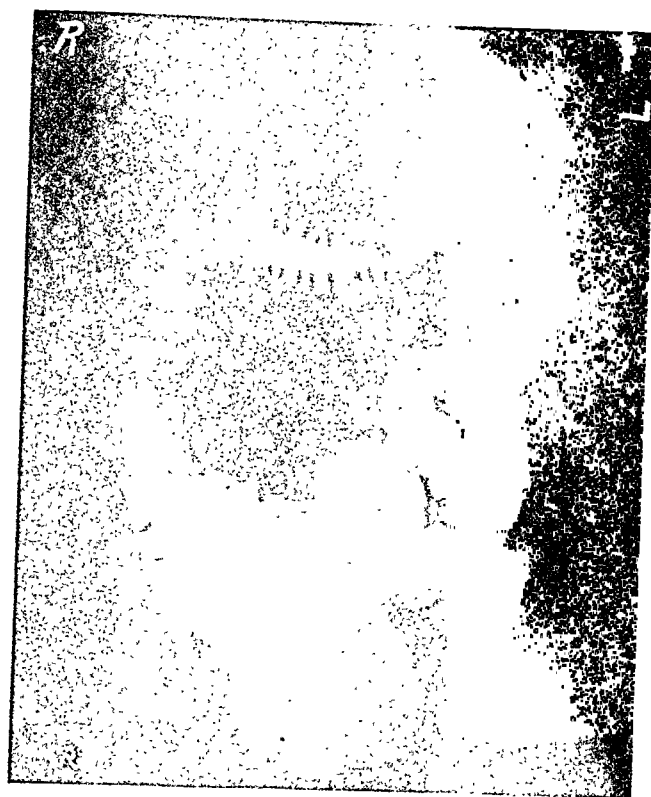


Fig. 21 (case XV) — Redundancy of the sigmoid and splenic flexure, with a deep hyperdescent of the cecum. Irregular colonic pattern. Female, 40, thin; past ileal resection for terminal ileitis. Also rectal operation.

redundant S. Romanum alone measured up to 110 cm. as against the average normal size of 60 or 80 cm. Stierlin stated that the length of the sigmoid may increase 2-3-4 times its average size, calling the higher degree: makrosigmoideum, the latter term being synonymous with the sigma elongatum mobile of Kienbock. It seems to us that there is no substantiation for such a generalized statement as contained in Stierlin's book, which, if true, would mean that the elongated sigmoid may reach the length of about 2.8 meters, a figure considered by Curschmann and also by Bryant as the maximal length ever encountered for the entire colon. Also our own x-ray observations on the redundancy of the sigmoid would consider such generalized description as exaggerated and unwarranted.

Hyperdescent of the cecum (dystopia coeci pelvica. Brosch, Curschmann, Stierlin) and cecum mobile as a subgroup of the redundancy of the colon, attracted too much attention in the past. Engel in 1857 noted cecal mobility in 10% of his autopsy material, a figure close to those found by Treves and Wandel. Sailer noted this occurrence in 20% of his office material, representing 320 cases. In Dreicka's autopsy material there was a common mesentery of the cecum and the small intestines, assuring a free movability of the former in 23% of the cases.

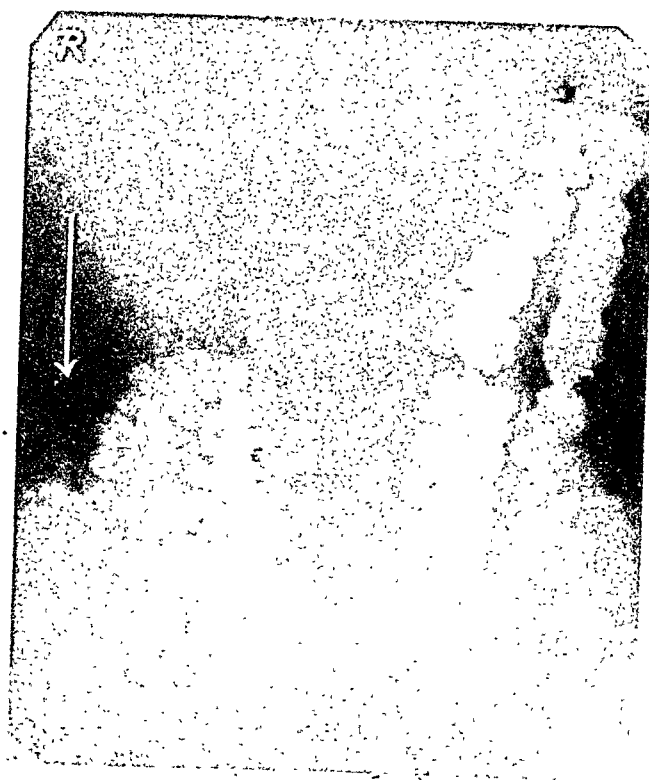


Fig. 22 (case XVI) — Inverted and redundant cecum and ascending colon, a horizontally tilted S shape, with 3 parallel branches. No constipation, nor other G. I. complaints. Mild neurosis. Female, 35, well built, stocky. Past operation for pyloric resection.

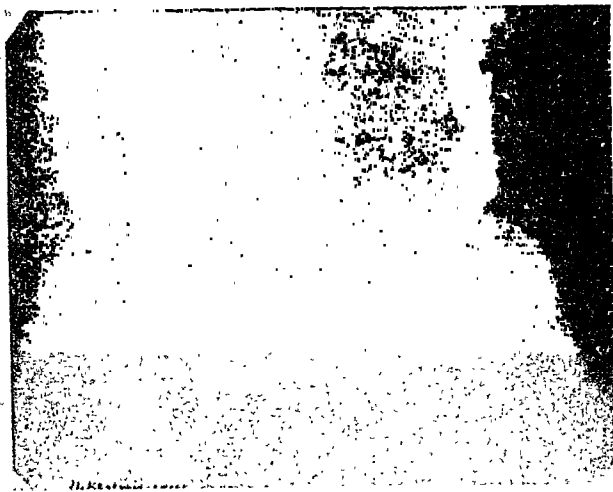


Fig. 23 (case XVII) — Redundancy of the inverted cecum and ascending colon, in a horizontally tilted S shape. The transverse is drooping. No abdominal complaints of importance. Female, 31, average build.

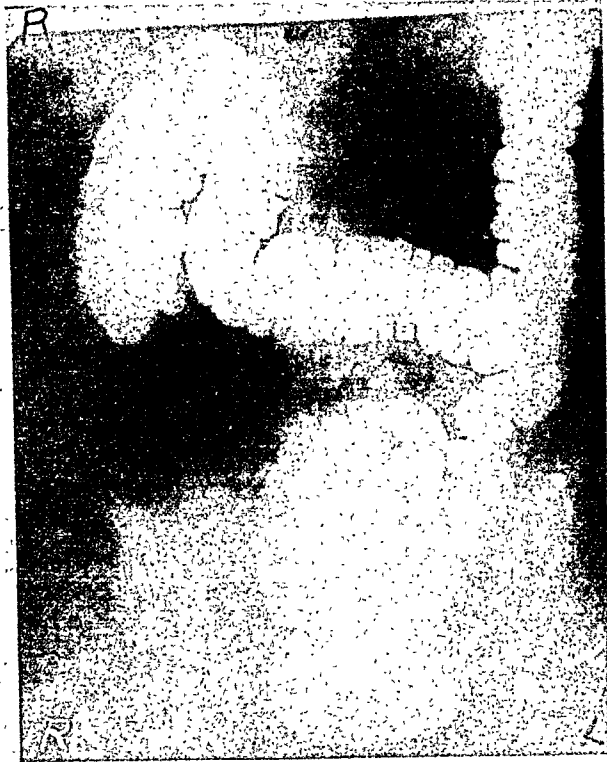


Fig. 24 (case XVII) — Cecum is hypodescendent now (dystopia coeci superior congenita, Brosch) in short straight line representing both the cecum and the ascending colon; with a high transverse. Redundancy of the sigmoid.

Hausmann established the clinical entity of the cecum mobile, purely on clinical observation. Wilms, Fischler, Klose and others followed it up by their surgical experiences. While Curschmann's "floating cecum"—rarely though—was responsible for some of the volvulus or obstruction cases, with a localization on the proximal colon (cecum and ascendens), Klose described cases in which the obstruction or volvulus of the same segment was brought about not by the

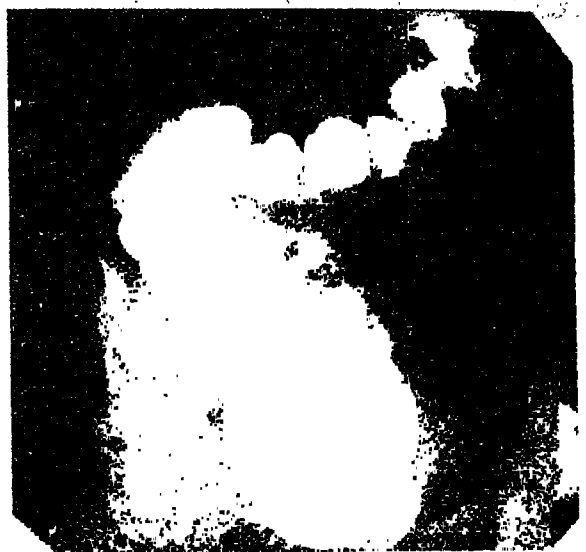


Fig. 25 (case XVIII) — Large pendular movement of the colon. High transverse with an upward curve. Twenty-four hours film.



Fig. 26 (case XVIII) — Seventy-two hours film. Transverse colon now deeply protic, due to an active free movement of the colonic segment. Male, 30, average build. Long standing complaints, referable to the stomach; constipation; persistent visualization of the appendix on the x-ray film.

free movability of that organ, but in contrast, by the fixation of the tip of the cecum by adhesive processes, counteracting a free movability of the gut.

Redundancy seems to occur at any age, with either sex, and without special preference to any habitus. It is true that LeWald, Carman, Soper, Feldman saw the asthenic type more often affected, others, however, experienced the opposite distribution. White stated the ratio in favor of the hypersthenics as against the asthenic was 2:1. Our own experience failed to favor



Fig. 27 (case XIX) — Redundancy of the transverse colon with a double inversion, a double V shape formation, together with a redundancy of the sigmoid and a hyperdescent of the cecum. No constipation. Symptoms of general weakness and neurosis. Female, 39, atonic type and underweight.

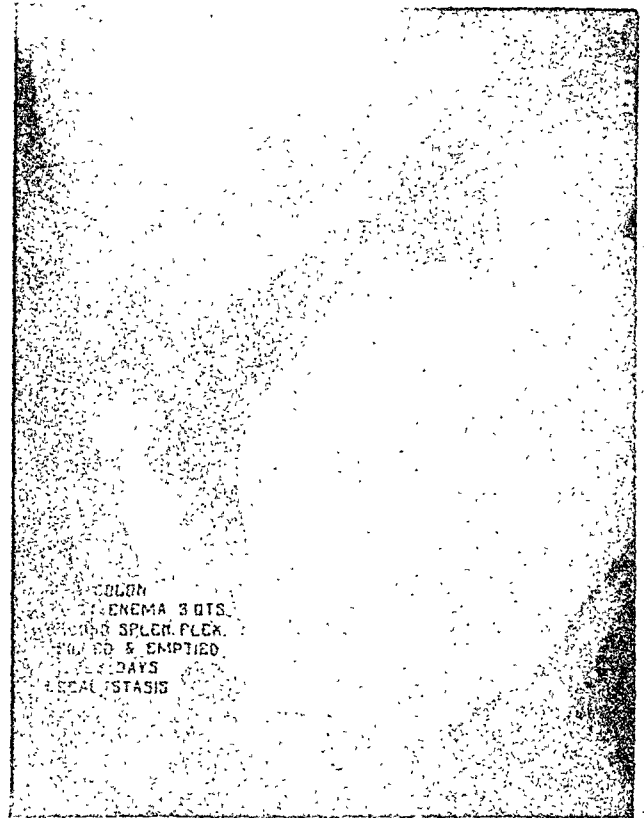


Fig. 28 (case XX) — Megasisigmoid. Three quarts of enema fluid fills colon only up to the splenic flexure. Megasisigmoid associated with redundancy of these loops. Female, 37, underweight, dehydrated, severely suffering from constipation, gas distress, vomiting, pain, 7 years. Loss of weight. Past appendectomy and cecoplication.

any age, sex, or habitus; the distribution among all these factors were more or less even, if anything, rather corroborative of White's observations, than that of the opposite group.

Carman states that "since the longitudinal muscle fibers are largely collected into the tenia, it is obvious that the tone condition of the tenia has much to do with the length and position of the colon at a given moment. Considered in this way, it may be that so-called redundancy is often merely an expression of atony." In theory, this sounds logically correct. In practice, however, several objections could righteously be made. According to the data in the literature, and also in our own observations, redundancy is not a disease of the atonic or hypotonic state. Hypersthenics are just as much subjected to it, or even more so. But even if redundancy would be an expression of a hypotonic state of the longitudinal musculature collected in the tenia, even then there is no anatomical reason why—as redundancy affects only certain parts in the colon—this loss of tone should be restricted to certain segments only, while others retain their tone fully. Furthermore, if under the intrainstestinal pressure, the atonic musculature is to yield at the weakened points of the tenia, passive dilatation and stretching of the structures in the thinned out walls would be expected to result. This is not the case in redundancy. In the redundant loops no signs of a structural stretching or thinning of the wall are noted, their vascular

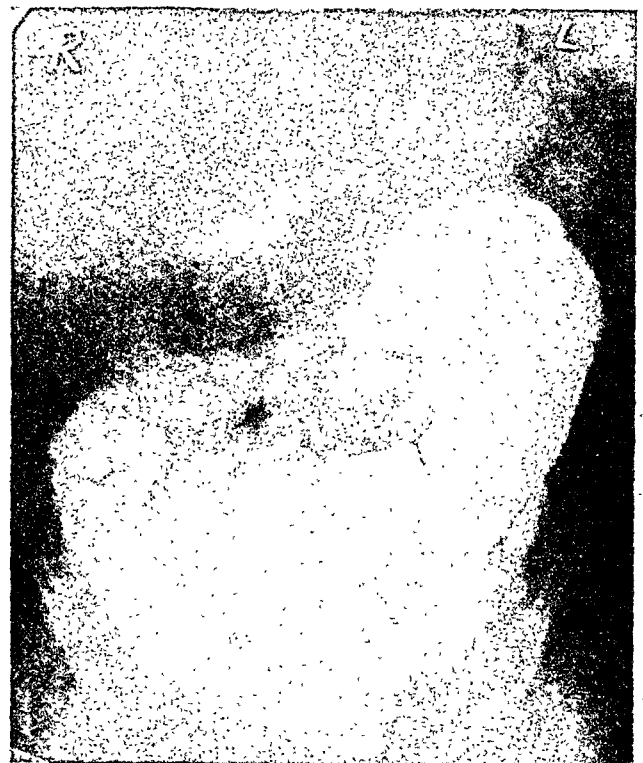


Fig. 29 (case XXI) — Megasisigmoid. without redundancy. Male, 44, average build. Complaints during last 7 years, constipation, vomiting, left sided abdominal pain, loss of weight. Had 4 major operations: appendectomy, cholecystectomy, gastric resection and repairs for the damages caused by foregoing operations.



Fig. 30 (case XXII) — Megacolon. Male, 30, average build. Suffering for the last 10 years, greatly aggravated since last year. Pain, gas-distress, meteorism, moderate constipation. Past operations for appendectomy and ileosigmoidostomy. Note and compare in last three cases the width of the colon, and the massive gas accumulation in the last case, with those in redundancy.

supply are equal to those of the non-redundant segments.

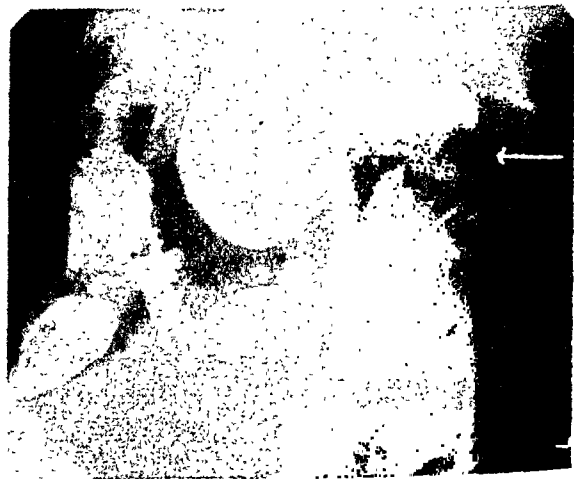
DIAGNOSIS

The diagnosis of redundancy of the colon is a roentgenological method. The procedure which is considered the only satisfactory one is the employment of x-rays in a three-phase method. 1) The most important phase of this series is the employment of the barium enema. This gives the morphological information. It shows the shape, position, size of the colon, with redundancy, if present. This method, at the same time, gives an approximate indication of the capacity of the colon by the measurement of the amount of the enema fluid needed to fill the entire colon. 2) The oral barium is the method of the functional diagnosis. In a great many cases the oral barium may pass through the intestinal canal, leaving the redundant loops without any trace or sign of the existence of redundancy. These are the well compensated cases, in which the motor mechanism is perfect and the patient usually does not suffer from the effect of redundancy. If, however, the breakdown of the motor power of the intestinal musculature interferes with the complete evacuation of the twisted or convoluted loops, then barium remnants and gas accumulation in some of

Right



Fig. 31 (case XXIII) — Redundancy of the sigmoid and descending colon. Note the redundant loops huddled together, in contracted form and reduced size, but with normal segmentation, haustration; teleologically a space-saving process. Female, 28, average build. Pain and cramps in abdomen. Past appendectomy.



(This film is laterally reversed.)

Fig. 32 (case XXIV) — Carcinoma of the descending colon, in a redundant loop, the segment undergoing large pendular movement. The eggsize tumor, at times easily palpable, becomes unrecognizable, when due to the large pendular movement, the segment creeps behind the thoracic cage, on the left side. Then again it moves out and becomes palpable. On account of the overlapping of the redundant loops, compression technic was needed to visualize the tumor, proven as adenocarcinoma. Patient survived operation after 5 years. High degree of kyphoscoliosis increased the puzzling effect of above conditions.

the loops or in some isolated knuckle will indicate the presence and the site of the redundant looping in a state of impaired motility. 3) A flat picture or scout film taken before the administration of the opaque material may reveal, especially in case of motor power impairment, the presence of gas accumulation. This may be

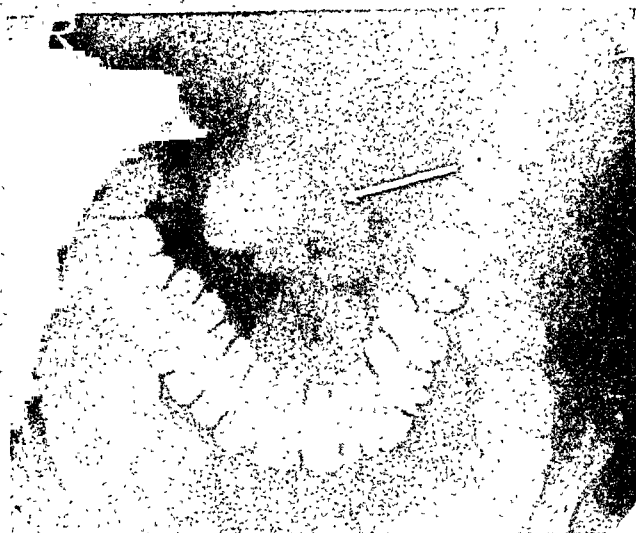


Fig. 33 (case XXV) — Redundancy of the colon, manifested on this film—a postdefecational film, after a barium enema—by a barium filled "knuckle" above the gastric region, without any gas envelopment, the colon showing on this particular exposure normal conditions. Female, 45, medium build, suffered among a variety of symptoms, from "gas-distress". Past appendectomy and operations on the genital organs.



Fig. 34 (case XXVI) — The colon, the stomach and duodenum are filled with gas, permitting a fairly clear visualization of these organs, including haustration, segmentation of the colon. This was an incidental finding in a case of a middle aged woman of average build, with a diagnosis of grand hysteria. There were no gastrointestinal complaints or symptoms.

located at any place or site in the abdomen, often far away from the suspected course of the colon, the most frequent location being the left splenic flexure or sub-diaphragmatic region.

Not rarely the entire colon may be visualized by the



Fig. 35 (case XXVII) — This film represents an incidental finding in a case of aerophagy, noted during the fluoroscopic examination of the chest organs of a young man. The normally haustrated colon was filled with gas to full capacity, permitting visualization of the colon nearly as clearly as one would obtain after a barium filling. A maximal degree of redundancy was incidentally noted on the gas filled colonic pattern. There were no gastrointestinal complaints or symptoms.

gas content of the gut, depicting its haustration, segmentation, loopings nearly as clearly as an opaque meal would. This gas-filling of the entire colon may be demonstrable, regardless of whether there is a redundancy in the colon, or there is none. Even in the former case the gas accumulation has no relation to the mechanism or dynamics of that of the gas-formation in the redundant segment.

The gas-filling of the colon, if associated with gas accumulation in the stomach and duodenum is often the result of aerophagy, a condition encountered in mental or hysterical conditions. The small intestines are always exempted.

The diagnosis of the redundancy of the colon is always simple and clear-cut. Failure of arriving at a correct diagnosis, either by not employing the x-ray method, or in case of its employment, by failure to properly correlate or appraise the x-ray findings will lead one to establishment of erroneous or unsubstantiated diagnoses, according to the prevalence of the individual complaints in the obscure symptomatology. White, Moeller, among others, enumerated some of the wrong diagnoses, for which the patients were treated or operated; these included appendicitis, peritonitis, cholelithiasis, nephrolithiasis, peptic ulcer, diverticulitis, carcinoma, fecal-tumor, intermittent tumor (according to the phase of loading or unloading). Of course the list is incomplete unless it also includes dyspepsia, irritable colon, colitis, nervous stomach, psychoneurosis,

ptosis and atony of the viscera, the plain case of intractable constipation and the so-called gas-distress. Often diagnoses of coronary sclerosis or even coronary thrombosis were erroneously made in such conditions. In lieu of the one, correct, diagnosis any of the aforementioned could be chosen and were actually made, "ad libitum".

It is surprising how often operations were performed in our series of cases. The majority underwent at least one major abdominal operation, but many of them had been subjected to major surgery twice, three, even four times. None of our cases had been operated for the correction of the redundancy. In hardly any of our cases was the presence of redundancy ever stated before, or known to the patient. The list of operations was headed by appendectomy.

DIFFERENTIAL DIAGNOSIS

Once the diagnosis is established by means of x-ray, no further scrutiny is needed as a rule. Knowing the normal patterns and giving allowance to certain physiological variations, any marked degree of extra looping, tortuosity, twist, kink, angulation, added and abnormal complexity in configuration of the colonic pattern, may be construed as signs of true redundancy.

There are certain configurations which are expressions of well known constitutional behavior. As Carman puts it: "certain types of frame-structures are constantly associated with definite types of visceral topography, just as facial characteristics distinguish races". In habitus asthenicus nearly all the viscera exhibit signs of drooping or ptosis and assume more of a longitudinal developmental pattern during the period of growth instead of a horizontal one. If, e. g., a deeply drooping V shaped transverse colon is encountered under such conditions, this type of configuration should not be considered a sign of redundancy. It should rather be considered a stigma of the underlying habitus. No doubt, that such transverse colons on repeated exposures, even giving allowance to the respiratory, positional and manipulative factors (Barclay, Holzknecht), will always show similar patterns, even if of various degree. If, however, a plethoric, or a hypersthenic type of man, with broad, stocky habitus, would exhibit a similar V shaped drooping transverse colon, this would not be compatible with the expression of the constitutional character. Here some other cause may be responsible for that.

If a V or any other shape of configuration of the transverse colon would change by its owner within hours or within a day or so into a widely different shape, position, or configuration, this active muscular function might be ascribed to a large pendular movement of the colon, a process due to the function of its intrinsic musculature (Reider, Stierlin, Galambos). In redundancy, however, a change in the shape or configuration would passively develop. Whenever a barium enema is employed, a change in the shape or configuration is immediately accomplished, not as a result of an intrinsic active muscular function of the colon,

but by an ever changeable passive process, as a result of the elongation of the colonic segment. The latter, due to its insufficient fixation, is loosely attached to the elongated mesentery, which permits free movability, a precondition to a redundant configuration.

The redundant colon has to be differentiated from the megacolon and megasigmoid. In Hirschsprung's disease the transverse diameter of the colon, especially that of the sigmoid, is extremely widened, and the lumen distended and the capacity of the enlarged bowel is manyfoldly increased. In the overwhelming majority of cases the process is limited to the sigmoid alone. The x-ray evidence should make the differentiation easy. Its association with redundancy is frequent. We present here the x-ray films of three cases of megasigmoid for comparative purposes.

Megacolon has actually been described by Hirschsprung in 1886 as megasigmoideum congenitum. In 1913 Neugebauer collected 169 cases from the literature. Only 32 out of this series presented the picture of full megacolon, and among them there were many without the participation of the flexures in the uniform enlargement. The majority proved to be megasigmoid. The wall of the sigmoid was often found to be hypertrophied to a large extent, even when no mechanical cause existed, such as a "Ventilverschluss" or "Ventilstenose" (valve-like closure or stenosis) (Assmann, Stierlin).

The mild and borderline cases are important from the differential viewpoint, inasmuch as delineation is desirable between the cases considered still normal and those already pathological in their patterns. However, this is not always easy. Individual evaluations in classification may play a role—a fact which should not be underestimated.

At times differentiation may encounter some difficulty, especially when additional morbid conditions are superimposed, or complicate the picture. A maximal spasm can be present, as in colica mucosa, or innumerable diverticula may beset the redundant loops, etc. Colitis may develop in a redundant segment. A redundant loop may harbor cancer, the recognition of which may be very difficult and at times recognizable only upon applying compression technique, as in the case presented here (See Fig. 32). In this adenocarcinoma of the sigmoid, there was in addition to the redundancy, a large pendular movement of the colon observed, as a result of which, the once palpated egg-size tumor, during the time of examination, suddenly disappeared hidden behind the thoracic cage, over the left side. Then it moved out again. Additional severe kyphoscoliosis still further reduced the space, a further complicating factor. Fig. 31 shows a uniformly contracted, "en miniature" picture of otherwise normally segmented, haustrated and configurated redundant loops in the descending colon and sigmoid—a space-saving process in teleological sense.

A point of differentiation concerning the changes in configuration of the redundant loops is made by the observation that redundancies and changes in colonic configuration due to redundancy are mostly observed

in the sigmoid, while the large pendular movements of the colon affect mostly the transverse colon.

SYMPTOMATOLOGY

Redundancy of the colon remains undiagnosed in the majority of cases. Kantor found that about 40% of the cases properly diagnosed as redundancy of the colon do not show any evidence of any disease. In the other 60% there are complaints, symptoms, sufferings. The finding of a still higher incidence of the symptomless cases is attributed to Curschmann, who in Stierlin's quotation expressed it as follows: "Absolute und scheinbare Vergrößerung. Umknickungen, Umbiegungen, Umlagerungen bei den meisten Individuen im Leben ohne jede Folge und Bedeutung sind, und lediglich einen zufälligen Befund auf dem Sektionstisch bilden." We purposely failed to express the incidence of the symptomless cases in our series in exact figures, because in the milder cases, and undoubtedly this comprises the majority, unimportant and unspecific symptoms are the common occurrence. These again are so common and trivial, that they are encountered in great many conditions, especially with nervous individuals, with and without redundancy of the colon. If such trivial symptoms happen to be registered with individuals, who incidentally show redundancy on the x-ray plate, there is no proof of any causal correlation between the symptoms and the redundancy.

Constipation is a frequent accompaniment. In Kantor's estimate 70% of the cases with redundancy suffer from constipation and 23% of the cases with constipation have redundancy. In his description the constipation, considered typical for this state, is commensurate with the degree of redundancy, and furthermore it is characterized by the fact that it tends to be present throughout life, and effects evacuation in great intervals, at times a week apart, without having the cumulative distressing feeling of the justly expected discomfort, in spite of the long stool interval. Moeller found constipation eight times out of a series of eighty cases. In our own observation we found constipation an eminent symptom, but not one of great diagnostic importance. We found constipation in redundancy of the colon not a more distressing or more frequent symptom than it is, e. g., in an average case of neurosis, without redundancy. The persistence of constipation throughout life, if present, would be explainable by the congenital character of the redundancy, a fact to be underlined even if redundancy often reaches its fullfledged clinical entity at some later age. The rare interval type of bowel movement, if present, may find its explanation by the fact that the redundant loops offer more room for the deposition and retention of the fecal matters than do normal or shorter colons, before eliciting a feeling of fullness or sending out emergency messages. Because of the chronicity of such states, a routine filling of the extra loops does not offer an unusual sensation for recording. We were not able to find these very unusual features in our cases of redundancy. They had constipation in most of the cases

for a number of years or months only, and they responded in no other way to dietary or medicinal regulations than cases with other types of constipation would.

While constipation is a fairly constant symptom in redundancy, there is no doubt, that this statement also works the other way around. Severe constipation, on account of its "vis a tergo" effect, must act also in developing and increasing retention, passive dilatation and elongation of the colon. A similar view is expressed by Feldman, who considers that the overloading of the sigmoid and the transverse colon as a result of constipation, is a factor in the etiology of the acquired type of redundancy.

Constipation does not necessarily cause any undue suffering in redundancy. If the bowels evacuate completely, whether spontaneously or under medicinal effect and the motor power of the intestines is intact, no real harm or suffering is expected to be forthcoming. Distress starts in the moment of the development of the impairment of the motility, resulting in a retention of fecal matters and of gas in the redundant loops. Kantor properly remarks that the loops do not represent fixed or static barriers or strictures, except if they are overfilled, displaced or distorted, then they develop a tendency thereto. Redundancy is not per se a colonic malfunction, it is only a predisposing factor for its development. Curschmann, Assmann, Stierlin, etc., expressed similar views.

Isolated gas islets somewhere in the redundant loops, with or without stagnation of the solid content are characteristic signs in redundancy and may serve as a cause or a potential cause for added suffering. Gas distress figured in 72% of Kantor's cases. The normal passage of gas or its retention may go hand in hand with that of the fecal matters. Besides the impaired transport gas-distress may be caused also by the mere presence of a kink, twist or ptosis of some of the loops, by shutting off mesenteric vessels whereby the absorption of the diffusable gases in the colon may be interfered with. Gases may be retained even after successful catharsis of the solid matters. Gas content of the entire colon, from other causes, due to aerophagy, is mentioned elsewhere (See Figs. 34 and 35).

Pain, if present, is considered a sign of deranged motor power of the intestines. Constipation, gas accumulation may cause pain, but the latter may be present also in absence of the former. The pain is a symptom of motor impairment. Muscular spastic contractions may try to overcome the motor disturbances. Kantor assumes that the pain is sharply localized at the site of redundancy and is due to superimposed spastic contractions. White emphasizes that the pain is located nearly always (in $\frac{3}{8}$ of the cases) at the right side, at the cecal region, even if the site of the redundancy is over the left side, as it usually is. This "throw-back" of pain also seems to be characteristic and important from the topical diagnostic viewpoint.

Most severe pain in association with systemic grave signs and symptoms may present itself even in the picture of an acute abdomen, when signs of impending

volvulus or intussusception develop. A twist or torsion of the elongated colonic segment sets in, followed by prostration and accompanied by signs of cardiocirculatory collapse, in the presence of a palpable abdominal resistance or tumor. Figs. 6 and 7 reveal the x-ray of the colon 36 hours after such an attack. The tremendous gas-filling at the hepatic flexure points to the fact that these redundant loops might have been the site of the torsion. Besides, there was a hyperdescent of the greatly mobile cecum, the vermiform appendix being projected in the center of the pelvis at the middle of the sacral vertebra.

Among the less typical symptoms diarrhea and vomiting figured with a 22-25% occurrence in Kantor's and Moeller's cases. Belching is a frequent symptom in redundancy. Kantor describes it as a misdirected effort to get rid of the gases from the splenic flexure. Moeller mentions eructation with many other, less characteristic and more heterogeneous symptoms which were observed in his cases. The manifestations were often characteristic for torsion, or volvulus-like syndromes or subchronic obstruction of the gut. Moeller reported three cases out of a series of 18, in which signs and symptoms of strangulation, twist of imperfect volvulus developed. Two out of three cases underwent a resection of the redundant colon. LeWald generally favors operative procedure whenever medical approach fails. The majority of authors counsel utmost conservatism.

My recent observations on two cases (the one mentioned above) may serve as a memento in consideration of the imminence of a surgical intervention. Both cases appeared clinically as acute abdomen of some unusual and obscure etiology. In both cases immediate surgical intervention seemed to be the method of procedure and as such it was seriously considered. In both cases, however, before it was too late, the tide turned and health returned unexpectedly, without surgery.

No doubt there are many other cases, similar in character, with unusual or puzzling features, when, during the critical period, the threatening symptoms and signs may suddenly regress or disappear altogether, and health returns, without surgery. Some of the cases reported in the literature, under various headings, as, e. g., when in peritonitis subserous plastic adhesions seemed to seal off the spreading inflammation, etc., might have belonged to such groups of incomplete torsion or volvulus. Nature's effort, supported by judicious administration of sedatives or antispasmodics, etc., might have effected a "restitutio ad integrum", without resorting to surgery, in cases when the development of a volvulus or strangulation has just been cut short and necrosis of the tissues averted, before the full torsion of the redundant gut completed the closure of the vessels. Besides the fully developed form of volvulus or obstruction, partial torsion, with regressive tendencies were mentioned by Assmann, Stierlin, Schwarz, Moeller, among others, especially in the sigmoid. The volvulus or occlusion, whether acute or chronic, complete or incomplete, may appear in the

symptomatology of pain, often of agonizing character, ileus, meteorism, "Darmsteifung", with visible intestinal peristalsis, vomiting, symptoms of acute intoxication.

In cases of actual volvulus the procedure is a surgical problem. The causal correlation between volvulus and redundancy has been clearly recognized and demonstrated on a large material, in a masterly way, by Curschmann in 1894.

COMMENT

1) Attention is called to the frequent occurrence of the abnormality known as redundancy of the colon, which is significant from medical, surgical, pathological and roentgenological viewpoints.

2) In a large percentage of cases redundancy exists without any symptoms or complaints. In such cases it represents an incidental finding.

3) Diagnosis is established by x-ray. A three-phase method has been suggested and described, and each individual part of this method has been appraised as to its respective value in the morphological, or in the functional phase of the diagnosis.

4) Redundancy of the colon requires as its basic precondition an elongated mesentery. Failure of sufficient fixation during the developmental process permits the loosely attached colon or colonic segment free mobility, similar to that prevailing with and typical of the small intestinal loops.

5) On repeated examination with the opaque enema we found the redundant colon showing an entirely different shape and configuration. A twist, a kink, a reduplication, etc., along the descending colon may at some later, repeated examination show a new, grotesque configuration along the sigmoid, while the descending colon has been restored to normal shape (see Figs. 14 and 15). Or, in some other case the picture of a horizontally tilted S shaped, inverted cecum without any ascending, but with a low transverse colon may at some other time change into a hypodescendent cecum with a short ascending and high transverse colon, the three parallel branches of the inverted cecum being straightened into the latter configuration (see Figs. 23 and 24). There are endless variations in the changeable, kaleidoscopic patterns along the redundant colon.

6) Failure of the free movability of the redundant loops, resulting on repeated exposures in a similarity or identity of the morphological appearance, is suggestive of a preexisting fixation due to adhesion, congenital or acquired, developmental or inflammatory (bands, ligaments, or membranes), more often over the right side of the abdomen.

7) Large pendular movement of the colon develops basically upon the same foundation, namely, upon the preexistence of an elongated mesentery. This, however, as indicated by its name, is a movement, an active process brought on by the function of the musculature of the colon. These slow, creeping, and wide-range movements result in pictures and configurations, widely different from each other (see Figs. 25 and 26). As against this, redundancy produces changes in the shape and configuration, as a result of a passively at-

tained incidental occurrence, and is due to the free movability of the loosely attached loops. The elongated mesentery, a developmental abnormalcy, is a prerequisite in both conditions. Both conditions may be present simultaneously. The large pendular movement most often occurs in the transverse colon, with the hepatic and splenic flexures serving as fixation points of the segment undergoing this active movement. Redundancy affects mostly the sigmoid, with the longest mesentery and the least posterior attachment.

8) Volvulus, as the most important complication in redundancy, also requires an elongated mesentery, for its development. Without redundancy, no volvulus; in redundancy, however, the occurrence of volvulus is extremely rare. Volvulus probably does not reach its full development in certain cases and may regress at any stage before finally peritonitis sets in, at a moment, when a complete closure of the vessels, which could result in gangrene of the affected area, still can be averted. Recognition of such states remains very difficult and important in the always puzzling picture of this pathology.

9) The most important problem in connection with redundancy of the colon is still the ascertainment of whether or not the case is well compensated, or is one

with impending or actually existing failure of motor mechanism. The breakdown in muscular compensatory mechanism will result in partial retention of both the fecal matters and gases. Gas retention may result from failure of its transport or of its absorption, or it may be newly formed in the stagnating and decomposed fecal material in the redundant loops.

Failure to medically correct the damages wrought by this chronic development may necessitate surgical intervention, especially in progressive cases. Establishment of a short circuit among the reduplicated and convoluted or twisted loops by exclusion and eventual resection of the chronically diseased extra loops should not represent an undue hazard in a well selected case, in the present era of surgery.

10) Proper recognition and management of the redundancy, especially by prevention of any possible breakdown in the compensatory mechanism may save suffering and prevent complication. It will enable the physician to properly appraise the situation. By properly diagnosing the case, he will avoid the embarrassment of relegating the case into one of the arbitrary or unwarranted groups of diseases. Even in the realm of the convolutions of redundancy the shortest way, seems to us, the straight way, through a good diagnosis.

REFERENCES

- Asmann, Herbert: *Klinische Roentgendiagnostik der Inneren Krankheiten*; 1924, 3rd Ed.; F. C. W. Vogel, Leipzig.
- Barclay, Alfred E.: *The Digestive Tract*. 1933, Cambridge, At the University Press.
- Brosch, A.: *Wien. M. Woch.*; 1910, pg. 1144-1155, 1210-1214, 1276-1283.
- Brown, Philip W.: *G. Blumer's The Therapeutics of Internal Diseases*; 1943, 3rd Ed.; Vol. IV; Appleton Co.
- Bryant, John: *Am. J. M. Sc.*; 1924, 499.
- Carman, Russell D.: *The Roentgendiagnosis of the diseases of the Alimentary Canal*; 1921, 2nd Ed.; W. B. Saunders Co., Philadelphia.
- Cecil, Russell L.: *A textbook of Medicine*; 1943, 6th Ed.; W. B. Saunders Co., Philadelphia, London.
- Curschmann, Hermann: *D. Arch. f. Kl. Med.*; 1894, Vol. 53; p. 1-44.
- Beckus, H. L.: *Gastroenterology*; 1944, W. B. Saunders Co., Philadelphia, London.
- Feldman, Maurice: *Clinical Roentgenology of the Digestive Tract*; 1945, 2nd Ed.; The Williams & Wilkins Co., Baltimore.
- Galambos, A.: *Am. J. Dig. Dis.*; May, 1944, Vol. 11, No. 5.
- Harvey, Samuel Clark: *Ann. of Surg.*, LXVII, No. 6. 1918, June, 641-686.
- Kantor, John L.: *Am. J. R. & R.*; 1924, Vol. 12, 414-430; *J. A. M. A.*, 1931, Vol. 97, No. 24, 1785.
- Larimore, J. W.: *Ann. Cl. Med.*, Vol. 1926, 439.
- LeWald, L. T.: *Disc. Am. J. R. & R.*, 1924, Vol. 12, 429.
- Meyer, Hermann: *Roentgendiagnostik in der Chirurgie*, 1927. J. Springer, Berlin.
- Moeller, Flemming, P.: *Acta Radiologica*, 1926, Vol. VI, Fasc. 1-6; Stockholm, P. A. Norstedt & Soener, 432-457.
- Sailer, Joseph: *Am. J. M. Sc.*, 1912, Feb.; Vol. 143; 157-172.
- Sauerbeck, Ernst: *Arch. f. Kl. Chir.*, 1909, Vol. 89; 873-881.
- Soper, Horace Wendell: *St. Louis, The Mosby Co.*, 1939.
- Stierlin, E. & Chaoul, H.: *Klinische Roentgendiagnostik des Verdauungskanal*, 1928, 2nd Ed.; J. Springer, Berlin, & J. F. Bergmann, Munchen.
- White, F. W.: *Tr. Am. Gastroenter.*, XXIX, 1927, 132-146; *Disc. Am. J. R. & R.*, Vol. 12, 1924, 429.

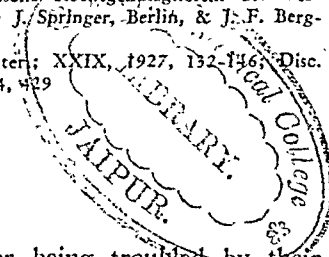
Editorial

SILENT GALLSTONES

IN 19 pages, reviewing 107 papers, of which he quotes the salient parts, Robertson proves that for the past four hundred years physicians have been aware that many patients who have gallstones are symptomless during their lifetime. In his own postmortem material of 1027 cases of gallstones, 627, or 61 per cent, were without any signs according to the search of their histories.

Robertson discusses the question what to do under these circumstances with a patient where by chance a gallstone was found. Has he to be operated upon when so many cases have carried their "heavy load" for

many decades without ever being troubled by their stones? This brings us to the question: why do many patients after "successful" operations have so many symptoms—afterwards? If you discuss this problem with a surgeon he is going to tell you of all those patients who had felt miserable for so many years, until, due to his skillful work, he was able to discharge them happily within a few days. The more out of town work this particular surgeon has, the better his results. For the patient is feeling fine, especially in the first months after the surgeon's action. But we know, that within the next few years, two-thirds of the patients have some of their symptoms again, luckily not always worse than before the operation. If the sur-



geon triumphantly hands you the stone-filled bladder from the operating table you feel, as a pure medical man, satisfied that the operation was a well advised one and that it was not like one of those appendectomies where you are waiting if the pathologist is able, after a long search, to satisfy your conscience with the report of "chronic inflammation," which was hardly detectable with the naked eye or the palpating finger. Yes, stones are in the bladder, and the organ is removed. The question arises only afterwards if this really was the cause for the complaints of the patient. It is my opinion that the poor results after cholecystectomy may be partially due, not to faulty technique or so called spasms in the common duct, as some authors think, but due to the fact that the removed gallstones were so called "silent stones." Gallstones are a pathological finding, but it may be that very often they were not at all the cause for the complaints of the patient. We should realize that the stone itself is a lifeless object, that only if it disturbs the gallbladder, or if it causes recurrent infectious processes, does it cause pains. Would it not be more sensible to look at it from a different point of view? It is a comparatively simple procedure to visualize gallstones by the roentgenological Graham test. It is more difficult to make the diagnosis of an inflammation of the gallbladder. The roentgenogram does not give much information in this respect. A poor concentration of the dye in the gallbladder can be due to many causes. The difference in the technique among the laboratories is also great, so that extensive experience is necessary to evaluate the findings. The short cut in thinking that the presence of gallstones means gallbladder disease is a treacherous one. I realize that it is often difficult to make the "modern" patient understand that the removal of his stone-filled bladder will not make him a well person. The patient living in a big city, reading the half-truths in his daily newspapers and his monthly magazines, will be inclined to consider that an operation will be the real cure for his suffering and that a physician who does not advise an operation is a man who is not up to date in his medical knowledge. It is a wide-spread observation that large, single gallstones are very easily visualized on the roentgen film, and that their removal is a comparatively simple procedure. However, a very high percentage of patients have a recurrence of their symptoms within a few months after their visit in the hospital. The question then arises: Why do people feel better in the first months after the operation? Most patients, if you scrutinize the histories, have never been in a hospital or in bed for

any length of time. They are often high-strung individuals, most of them are indiscriminate eaters. "Of course," they will tell you, "I have indigestion now and then, but generally I take some bicarbonate or some other radio-advertised medicine and then I am relieved."

Being admitted to the hospital, they have to stay in bed, get their meals at regular intervals, have the care of competent nurses, and, last but not least, the patients' bowels are regulated. Especially people who have been eating their lunches in cafeterias or on lunch-counters for years, give their digestive organs the first decent treatment in many years. No spices, no cold sandwiches, no alcohol. Although all this is only a two-weeks affair, it does wonders to their intestinal tract. Is it astonishing, that the patient feels better for several months after cholecystectomy?

After that period some of the patient's symptoms reoccur. As the surgeon has nothing to remove any more, the patient is referred back to his general practitioner or gastro-enterologist, — and now the trouble starts. What can we do? Which organ can we blame for the recurrent trouble? We speculate, we try the entire list of all those preparations known or advertised. The "post-cholecystectomy syndrome" has begun and is going to haunt us for many years to come.

Weiss, nearly thirty years ago, expressed this in excellent words: Postmortem records abundantly show that the presence of gallstones is not inconsistent with long life, and they have been found in large numbers in the gallbladders of those who have never during life suffered any pains or discomfort that led to a suspicion of their existence. If every individual in whose gallbladder or bile ducts are gallstones, suffered the agonies of biliary colics "peace on earth" would be impossible. Weiss adds: If stones could be kept at rest and inflammation prevented, surgical treatment would be unnecessary.

We can only agree with Weiss. It should be our endeavor to determine in every case if the gallstones seen on the roentgenogram are "silent" or trouble making ones. And it might not be a bad idea to have the silent ones also treated with silence — towards the patient, for if the patient is not aware of the concretions, which he or she is carrying around for many years, then it might be easier for him to get over certain discomforts of indigestion without being frightened after every meal. Robertson's article gives us an opportunity to review our thinking in cases of "silent" gallstones. Often enough, but never too often, has this been brought to our attention during the past four hundred years. — Franz J. Lust.

REFERENCES

1. Robertson, H. E.: Silent Gallstones. *Gastroneterology*, 5, 5, 345. November, 1945.
2. Weiss, Samuel: Gallstones. *New York Medical Journal*, 107, 932, 1022; 1918.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
E. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
*J. EDWARD BERK
J. E. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEATHER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

* With the Armed Forces.

CLINICAL MEDICINE

STOMACH

FLETCHER, C. M. AND JONES, F. A.: *Risks of gastrosocopy with flexible gastroscope.* (Brit. Med. J., p. 421, Sept. 29, 1945).

The authors emphasize that gastrosocopy should be performed only by those experienced in the use of the flexible gastroscope and who are aware of the risks. They report two deaths which were probably due to gastrosocopy and report having had pain and fever in four other cases. Seven other cases of esophageal perforation, five of which ended fatally, are cited. Of the authors' two fatalities, one case had had scurvy. The tissues were very susceptible to damage and passage of the gastroscope should not have been undertaken. In the second case perforation resulted from exerting pressure when the instrument tip was in the hypopharynx. — F. E. St. George.

BOWEL

LUBITZ, J. M. AND FLYNN, R. W.: *Chylangioma cavernosum mesenterii.* (Surgery, v. 18, p. 772, Dec. 1945).

Tumors of the lymph vessels belong to the rarest of neoplasms and those occurring in the mesenteric vessels are the least common of all. The authors found five cases of chylangioma cavernosum reported in the literature and present a sixth case of their own.

These are benign tumors occurring in the lymphatics of the mesentery of the small bowel. Symptoms of a tumor and obstruction may be present if the tumor is of sufficiently large size. Erosions and bleeding may be complications. The tumor may be the site of secondary infection. In five of the six cases reviewed the tumors also included the mucosa of the intestinal wall. The origin and derivation of these tumors are still unknown. — F. X. Chockley.

LIVER AND GALLBLADDER

POLLOCK, M. R.: *Liver function in infective hepatitis gauged by hippuric acid synthesis tests.* (Brit. Med. J., p. 878, Dec. 22, 1945).

The hippuric acid test was employed serially in 81 cases admitted to hospital with infective hepatitis. Serum bilirubin levels were also determined. The patients were admitted to hospital usually within three days after onset of jaundice and tests were begun soon thereafter.

Although the ability of the liver to synthesize hip-

puric acid was related to the severity and stage of the disease, it was not related to the serum bilirubin level. Improvement in hippuric acid synthesis was frequently shown by patients in whom the serum bilirubin levels kept rising and the jaundice became more intense. Apparently the liver damage is greatest before the icterus stage and consequently specific treatment would have its best effect only if begun before the patient shows jaundice. — F. E. St. George.

ULCER

CARRYER, H. M. AND PRICKMAN, L. L.: *Brucellosis and peptic ulcer.* (Proc. Staff Meet. Mayo Clinic, v. 21, p. 11, Jan. 9, 1946).

The authors briefly review the epidemiology of Brucellosis, stressing its association with milk and the fact that *B. abortus*, varieties *bovis* and *suis*, more frequently causes endemic undulant fever in the United States than does *B. melitensis*. The association between Brucellosis and peptic ulcer was studied, as this type patient consumes large quantities of milk and has an abrasion on the gastro-intestinal mucosa which might serve as a portal of entry for such an infection. Using a titre of 1:80 as signifying infection with the *Brucella* group, 82 cases were diagnosed in 1944. Of these, 11% had a duodenal ulcer. In a control group of 221 cases, with no evidence of Brucellosis, 4% had a duodenal ulcer. The authors feel that, in view of the low number of cases and the fact that routine roentgenographic studies were not performed on all of the cases listed, no statistically significant conclusions can be drawn, although a trend is indicated. — E. J. Tallant.

THERAPEUTICS

HERMANN, G. R. AND ROCKWELL, P. A.: *Reversible and irreversible disease of the liver with reference to effect of choline.* (Texas State J. Med., v. 41, p. 288, Oct. 1945).

The study was made on 32 cases of hepatic cirrhosis, six of which are reported in detail. The simplest indication of liver damage was a low serum albumen. Therapy consisted of high protein diets with large amounts of choline. Excellent responses were noted in patients with enlarged livers due to alcohol and dietary deficiencies. In two cases of chronic hepatic cirrhosis with shrunken livers and ascites the response to choline administration was poor. Patients with congestive heart failure also improved on the high choline intake. Apparently choline has not only a lipotropic effect on

the liver but also improves myocardial efficiency presumably by converting cholesterol deposits to phospholipids. — D. A. Wocker.

SURGERY

GILJE, L. E. AND LAMPSON, R. S.: *Acute appendicitis in amebic dysentery.* (U. S. Naval Med. Bull., v. 46, p. 102, Jan. 1946).

Acute appendicitis in amebic dysentery has been encountered only seldom in the United States. The condition is a difficult one both as to diagnosis and treatment. The symptoms may be obscured by dysentery, and surgical wounds of the infected amebic intestine heal with reluctance. The frequency of appendiceal involvement in intestinal amebiasis in the lining is unknown but post-mortem examinations give an incidence of 7 to 40 per cent. Appendectomy may be accompanied by a high mortality rate (41 per cent in the Chicago epidemic of 1933).

Intensive treatment of the dysentery is essential to insure healing in the appendiceal stump if appendectomy is performed. The authors believe that in most cases of appendectomy in acute amebiasis the diagnosis will not have been made until after the operation. — G. N. N. Smith.

EATON, C.: *Amputative hemorrhoidectomy: important surgical landmarks of anorectum.* (Western J. Surg. Obstet. Gynecol., v. 53, p. 386, Nov. 1945).

The author deplors the lack of definitive anatomic landmarks for guidance in amputative operations for hemorrhoidectomy. He makes a number of suggestions to determine by surgical landmarks the anatomic level at which excision of the prolapsing hemorrhoid tissue should be carried out. These landmarks may be determined by palpation of the wall of the anal canal and include the divisions of the sphincter musculature as well as the various sheaths of the conjoined longitudinal muscle that give rise to these divisions.

CASTRO, A. F. AND KIERNAN, P. C.: *Extensive resection of perforating carcinoma of the stomach with abscess.* (Proc. Staff Meet. Mayo Clinic, v. 21, p. 15, Jan. 9, 1946).

The authors cite a case with a 20 year history of epigastric pain, relieved by food with periodic exacerbations and remissions. Following a poor response to a medical regimen an exploratory laparotomy was performed with a preoperative diagnosis of a large abscess cavity communicating with the lumen of the stomach, based on roentgenographic studies. A large fluctuating mass was found adherent to the stomach, transverse colon and its mesocolon, the undersurface of the right lobe of the liver, pancreas and duodenum. Biopsy revealed a grade 3 carcinoma, this diagnosis being later confirmed by pathological examination of the resected tissue. The mass was dissected free from the liver, first portion of the duodenum, pancreas and splenic vessels. The involved portion of the transverse colon was resected with its mesocolon and a high subtotal gastrectomy was performed, removing the entire mass. A double-barrel colostomy was formed from the two limbs of the transverse colon. The authors stress

the long history of the case and the necessity of early diagnosis if curative surgical procedures are to be undertaken. At the present time no more than 25% of all gastric carcinomas observed can be removed and the five year survival rate of gastric carcinoma is 7%. — E. J. Tallant.

EXPERIMENTAL MEDICINE

ABSORPTION

VISSCHER, M. B. AND ROEPKE, R. R.: *Influence of induced changes in blood plasma osmotic activity on intestinal absorption.* (Proc. Soc. Exper. Biol. Med., v. 60, p. 1, Oct. 1945).

Experiments were performed on nembutalized dogs provided with adjoining ileal segments. Equiosmotic solutions of sodium chloride and sodium sulfate were introduced into the loops. Changes in osmotic activity of the blood were produced by intravenous injection of 100 cc. of 5 per cent sodium chloride.

The hypertonic salt solution injected intravenously resulted in raising the osmotic activity of the intestinal loop fluids to above that of the pre-injection plasma osmotic activity. In control experiments such increases in gut fluid osmotic activity were never observed. After the plasma osmotic activity had become elevated the gut fluid values did not rise as high as before elevation was produced. The osmotic gradient between plasma and intestinal epithelium therefore is not the prime factor determining the direction of water transfer through the intestinal epithelium. — I. H. Dougherty.

PHARMACOLOGY

MASSON, G. M. C. AND BELAND, E.: *Influence of the liver and kidneys on the duration of anesthesia produced by barbiturates.* (Anesthesiol., v. 6, p. 483, 1945).

The role of the liver and kidneys in the detoxication of barbiturates and their influence on the duration of anesthesia was studied. Twenty-nine barbiturates were investigated. The authors found that nembutal, secenal, evipal and thioethamyl are detoxified mainly in the liver. Barbitol and phenobarbital are detoxified mainly in the kidney. Dial and neonal are detoxified by both liver and kidney in about equal proportions. Pentothal and some other barbiturates were found to be detoxified in tissues other than the liver and kidney. — G. Klenner.

PATHOLOGY

HIMSWORTH, H. P. AND GLYNN, L. E.: *Gross chemical changes in the liver in dietetic necrosis.* (Biochem. J., v. 39, p. 267, 1945).

Rats on a low casein diet have been shown to develop necroses of the liver. The lesions can be produced with certainty by feeding diets containing proteins poor in sulfur amino acids.

The livers of rats with acute necrosis of dietary origin show increased amounts of water and protein and an absence of glycogen. Liver fat is unrelated to the development of the necroses. Livers with healed necrotic lesions show normal values for water and protein content. The composition of the liver alters suddenly and coincidentally with onset of cellular damage. — M. H. F. Friedman.

The Isolation and Testing of Fecal Streptococci

By

GEORGE H. CHAPMAN

NEW YORK, NEW YORK

CLEARER understanding of the role of different streptococci in gastrointestinal diseases depends upon satisfactory methods for isolating and testing them. "Blood agar" is an unsatisfactory isolation medium, even when sodium azide is incorporated in it. Treatment with sodium carbonate likewise is unsatisfactory because it destroys most streptococci but preserves enterococci, most of which have no pathologic significance. The discovery of an isolation medium (1) which almost completely inhibits all other bacteria, which gives about 50 per cent more colonies in tests of pure cultures than does "blood agar" and which differentiates the three main groups of intestinal streptococci has resulted in new appreciation of their significance. In addition, the application of resistance tests (2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13) permits appraisal on the basis of the toxigenic properties of the organisms, which would appear to be significant because to produce tissue damage the organisms would be expected to elaborate some sort of toxin. Finally, the finding that, in the absence of achlorhydria, the number of *Escherichia coli* is inversely, and the number of paracoli is directly, proportional to the severity of the streptococcal intoxication (3) increases the diagnostic significance of the tests. When these methods are combined with the newer procedures for isolating and testing intestinal pathogens and the recently developed method for isolating pathogenic staphylococci (14) it is possible to determine the role of different fecal bacteria with a higher degree of precision than has been possible by previous methods.

The isolation of streptococci from feces

The modified new medium for the isolation of streptococci is prepared as follows:

Water	1,000 ml.
Bacto tryptose	10 grams
Bacto proteose no. 3 peptone	5 grams
Bacto proteose peptone	5 grams
Sucrose (table sugar is satisfactory),	50 grams
Bacto agar	15 grams
Dextrose	1 gram
K ₂ HPO ₄ , anhydrous	4 grams
Trypan blue, 1.0%	7.5 ml.
Crystal violet (C. C.) 0.10% based on dye content	0.8 ml.

Sterilize as usual. Cool. When comfortably warm to sensitive areas of skin add potassium tellurite and pour 40 plates from the liter of medium. Because the

optimum amount of tellurite is critical the Difco Laboratories have prepared a large amount of solution and the author has determined the amount to use in this medium. They have also prepared the culture medium in dehydrated form without the tellurite which is to be added when ready to pour.

To isolate streptococci and other bacteria, add water to the feces until it is just soft enough to pipette. Make six ten-fold dilutions and determine the proportion of solids by drying at 100° C. Spread 0.01 ml. of each dilution on different culture media as follows:

7.5% sodium chloride phenol red mannitol agar —
dilution no. 1.

Streptococcus medium — dilutions nos. 1, 2, 3, 4.

Levine's eosine methylene blue medium —
dilutions 1, 3, 5, 6.

MacConkey's agar — dilutions 2, 4.

Intestinal pathogen media — appropriate dilutions.

Incubate the streptococcus medium, Levine's and MacConkey's media exactly 24 hours (not "overnight") and the phenol red mannitol agar for 36 hours and calculate the number of different colonies on the basis of millions per 100 grams of dry feces.

The following types of colonies will be noted on the streptococcus medium:

Enterococci produce dark blue or black slightly raised colonies about 1 mm. in diameter.

Streptococcus salivarius (most nonhemolytic fecal streptococci fall into this group) produce blue "gum drop" colonies about 2 or 3 mm. in diameter, depending upon how crowded they are.

Streptococcus mitis (most "*Streptococcus viridans*" fall into this group) produces small or minute blue colonies.

Other streptococci have not been studied sufficiently to determine their characteristics on the medium.

In the occasional instance where coliforms grow on the medium they produce gray or brown colonies. Only rarely is a "spreader" encountered. However, they may grow but not spread, making it imperative not to touch gray or brown colonies or a spreader may be carried with the streptococci. With few exceptions, the coliforms that do not grow are actually killed. Hence, only about 8 per cent of the streptococci isolated are contaminated by coliforms even though the streptococci may have been outnumbered 1 million to 1. By this method, streptococci may be found in about 95 per cent of fecal specimens from chronic invalids.

Because very few enterococci are pathogenic, it is

important to differentiate them from other streptococci, which are frequently pathogenic. At the present time it is impossible to determine pathogenicity of enterococci except, possibly, by animal inoculation experiments. Since they are easily recognized, grow well under unfavorable conditions and usually produce large green zones on blood agar they are usually mistaken for "streptococci" or "*Streptococcus viridans*." This is true, particularly in sodium carbonate treated specimens. Hence, the value of the present method.

Since streptococci are not significant in feces unless they produce local or systemic tissue damage, it is desirable to try to establish their toxigenicity. Intradermal tests and the "pathogen-selective" method are not sufficiently precise and complement fixation and agglutination reactions appear to be quite lacking in specificity.

A number of bacteriologists have shown that with typhoid bacilli, meningococci, *Hemophilus influenzae*, staphylococci and P-hemolytic streptococci, power to grow in fresh defibrinated blood is related to pathogenic properties of the cultures. We (2, 3, 4, 5, 6, 9, 11, 12, 13) have shown that a similar relationship holds for the types of streptococci under discussion. We also showed (7) that resistance to the bactericidal action of fresh blood was parallel with resistance to precise dilutions of certain antiseptics. We now employ hexylresorcinol and have established similar relationships including a parallel with the dermonecrotic power of the bacterial suspensions which indicates that it is related to the toxigenic properties of the cultures. A similar relationship had been shown for P-hemolytic streptococci (15).

The application of resistance tests has opened up an entirely new appreciation of "intestinal intoxication," which will be presented in detail elsewhere. Briefly, the proportion of toxigenic variants is a measure of the intensity of intoxication by the species of streptococcus studied. This had been shown to be true of dental infections (11, 16) and is related to the blood sedimentation rate, nonfilament-filament ratio of leucocytes and the severity of the illness (13).

There are so many technical details that contribute to the accuracy of the results that presentation of technical data is delayed until they can be adequately presented. A few of them will be discussed here.

Streptococcus mitis and *S. salivarius* cultures are not homogeneous mixtures of cells but are kaleidoscopic mixtures of rapidly changing dissociants or variants. Whenever a highly toxigenic streptococcus is taken from the body and cultivated on artificial culture media it gradually loses pathogenic properties such as elective localizing power, toxigenicity and virulence by "degeneration" of some of the dissociants. In some cultures this degenerative process is so rapid that they become nonpathogenic within a few days. Where a culture may contain 100 per cent of resistant variants at the time of isolation, it may contain a negligible number a few days later.

A second degenerative trend lies in changes probably associated with pH and accumulation of metabo-

lites. If a culture in broth is incubated it will not multiply for a short while (the lag phase), then it will multiply rapidly (the logarithmic phase) until it has used up the nutrients and will then cease to multiply (the stationary phase). During the logarithmic phase (i. e., when the culture is becoming quite cloudy) the individual cells are most resistant to the antiseptics mentioned previously but they lose this resistance soon after the stationary phase has been reached. Consequently, we have obtained a much higher proportion of resistant dissociants and an improvement in antigenicity by watching the growths hourly after the time when the earliest ones are expected to become cloudy (6 hours for *S. salivarius* cultures and 10 hours for *S. mitis* cultures).

A third type of loss of pathogenicity is associated with ingredients of the culture medium. Not all "broths" are satisfactory for optimum toxigenicity. Of the commercial dehydrated products, Bacto brain heart infusion gave best results. However, it could be improved by the addition of other peptones and extra phosphate. If too much is added, growth is unduly retarded. Best results were obtained by adding the following combination of ingredients to each liter of Bacto brain heart infusion:

Bacto proteose no. 3 peptone	2.5 grams
Bacto tryptose	2.5 grams
K ₂ HPO ₄ , anhydrous	2.0 grams

Determining the resistance of streptococci

The preparation and testing of resistance of streptococcus growths is done as follows: A platinum inoculating needle is hammered at the tip to make it in the shape of a spear. This is used to cut around the colonies so that whole colonies may be transferred to the "toxin broth," giving pure cultures more rapidly than by usual methods. About 10 *S. salivarius* and 10 *S. mitis* colonies are selected for study. Each is cut from the streptococcus medium and put into a separate tube of the toxin broth and incubated at 37° C. *S. salivarius* cultures are observed hourly after 6 hours and *S. mitis* cultures are observed hourly after 10 hours. If a bacteriologist is not available during the night cultures may be transferred to the refrigerator by an assistant as soon as they become sufficiently cloudy and examined by the bacteriologist not later than 8 hours afterward or the original inoculated broth tubes may be put into an incubator kept below 20° C. and a time switch set to turn on the heating coils about 7 hours before the bacteriologist starts work.

The growths will be of two types, uniformly cloudy or sedimented with less cloudy or clear supernatant. When the resuspended sediment is below standard cloudiness, sufficient supernatant may be decanted to provide a suspension of standard turbidity. If the uniformly cloudy culture does not become sufficiently turbid the amount taken for testing must be proportionately increased. With growths of standard turbidity, a loopful is mixed aseptically with 0.5 ml. of 1:125,000 hexylresorcinol ("S. T. 37" diluted 1:125).

shaken thoroughly and a loopful streaked half way across a plate of blood agar to serve as a control and to check on hemolysis and purity (the toxin broth cultures are then left in the refrigerator until the resistance tests have been completed). Exactly 110 minutes later the inoculated mixture is shaken again and another loopful is streaked on the blood agar. The blood agar is incubated 20 to 24 hours and the growths compared. Cultures that give as dense a growth after treatment with hexylresorcinol as they do with the control are highly toxigenic and are suitable for use in vaccines.

The proportion of resistant variants is determined from the number of colonies tested and the number found resistant and from this proportion the total number of resistant colonies in the original feces may be calculated. The resistant cultures are pooled in case they may be needed for the preparation of a vaccine, and the vaccine suspension made immediately. Any delay will result in degeneration of the antigenic structure with consequent loss of potency of the vaccine.

Interpretation of results

Escherichia coli. When the total number of *Escherichia coli* is above 1,000,000 millions per 100 grams of dry feces it is probable that the patient has achlorhydria. With this exception, the more the number is below this value the more severe the intoxication. The average chronic invalid showed 41,460 millions per 100 grams of dry feces.

Paracoli. The total number of *paracoli* is directly

proportional to the severity of the intoxication, with the average chronic invalid showing 4,225 millions per 100 grams of dry feces. The ratio of coliparacoli also reflects the severity of the intoxication. While it may be an average of 300:1 in nontoxic cases it averages 1:1.5 in toxic cases (2).

Streptococcus salivarius. The average number of toxigenic variants of *S. salivarius* was 1,932 and the average proportion was 42 per cent of the total. The higher the percentage above that the more severe the intoxication.

Streptococcus mitis. The average fecal count of toxigenic variants of *S. mitis* was 5,805 millions per 100 grams of dry feces which was an average of 62 per cent of the total *S. mitis*. These values are considerably higher than those of *S. salivarius*.

Because pathologic conditions of the gastrointestinal tract often are the result of upper respiratory tox-infection acting either through the autonomic nervous system or from contact with swallowed toxins (3) "intestinal intoxication" is not always reflected in changes in the fecal flora. In other instances the intestinal staphylococci and streptococci are merely progeny of upper respiratory bacteria that have survived passage through the stomach and duodenum.

In addition changes in the fecal flora may be obscured by the fact that the more severe the intoxication the greater the suppression of intestinal bacteria. On the contrary the longer the feces in the lower intestinal tract the higher the number of bacteria. These factors illustrate the caution necessary in interpreting results of bacteriologic examinations of the feces.

REFERENCES

1. Chapman, G. H.: The isolation of streptococci from mixed cultures. *Jr. Bact.*, 48:113-114, July, 1944.
2. Chapman, G. H. and Lieb, C. W.: Bacteriology of the intestinal tract in certain diseases. II. The possible inhibition of colon bacilli by pathogenic streptococci and staphylococci. *Rev. Gastroent.*, 5:234-240, September, 1938.
3. Lieb, C. W. and Chapman, G. H.: Bacteriology of the intestinal tract in certain chronic diseases. III. The possible role of upper respiratory infection. *Rev. Gastroent.*, 5:306-318, December, 1938.
4. Rawls, W. B. and Chapman, G. H.: Experimental arthritis in rabbits. Comparison of the arthritis-producing ability of unagglutinable streptococci which resist the "bactericidal" action of fresh, diluted defibrinated guinea pig blood and those which are agglutinable but sensitive to the "bactericidal" agent. *Jr. Lab. & Clin. Med.*, 21:49-66, October, 1935.
5. Chapman, G. H., Staley, M. H. and Berens, C.: The isolation and in vitro testing of pathogenic types of non-exotoxigenic streptococci. *Ann. Jr. Clin. Path., Tech. Suppl.*, 1:20-27, Jan., 1939.
6. Ruggers, J. C. and Chapman, G. H.: Newer bacteriologic considerations of dental infections as factors in systemic disease. *J. Tenn. State Dental Assn.*, 21:149-158, September, 1941.
7. Chapman, G. H. and Rawls, W. B.: Studies of streptococci. I. Qualitative differences in resistance to various agents. *Jr. Bact.*, 51:323-331, April, 1936.
8. Chapman, G. H. and Carey, L.: Studies of streptococci. II. Quantitative differences in resistance to sodium bicarbonate and hexylresorcinol. *Jr. Bact.*, 51:333-337, April, 1936.
9. Chapman, G. H., Berens, C. and Nelson, E. L.: Studies of streptococci. III. Preliminary attempts to correlate resistance to chemicals, etc., with pathogenic effects. *Jr. Bact.*, 51:339-346, April, 1936.
10. Chapman, G. H.: Studies of streptococci. IV. Resistance of enterococci. *Jr. Bact.*, 52:41-46, July, 1931.
11. McCall, J. O. and Chapman, G. H.: The health hazard of decaying teeth in children. *Jr. Am. Coll. Dentists*, 17:65-71, March, 1943.
12. Chapman, G. H., Berens, C., Lieb, C. W., Rawls, W. B. and Staley, M. H.: Examination of cultures from persons suspected of having chronic infection. *Ann. Jr. Clin. Path.*, 2:401-405, July, 1939.
13. Staley, M. H. and Chapman, G. H.: Probable pathogenic streptococci and staphylococci in chronic low grade illness. An analysis of their frequency in three hundred and non-toxic cases. *Arch. Otolaryngol.*, 51:454-466, March, 1941.
14. Chapman, G. H.: Staphylococci in autoimmune therapy. *Ann. Jr. Dent.*, 12:169, December 1945.
15. Todd, F. W.: The virulence of hemolytic streptococci. *Bact. Jr. Exper. Path.*, 4:189-202, February, 1927.
16. McCall, J. O. and Chapman, G. H.: Pathogenic pathogenic streptococci in carious teeth in children. In preparation.
17. Chapman, G. H.: Seasonal variation in the bacteriology and hematology of persons with low grade chronic disease. In preparation.

A Method for Bio-Assay for Extracts Which Inhibit Gastric Secretion

By

M. H. F. FRIEDMAN, Ph.D.

PHILADELPHIA, PA.

and

D. J. SANDWEISS, M.D.

DETROIT, MICH.

IN THE study of the inhibitory effect of various extracts of urine and tissues on gastric secretion, one of the difficulties encountered has been the absence of a simple method for the assay of potency. In the procedure commonly in use, testing on gastric pouch dogs, a great drawback has been the development of refractoriness to certain tissue extracts. In addition, when using the pouch dog there is always the distinct limitation to the number of assays which may be carried out within short periods of time.

It occurred to one of us (M.H.F.F.) that a satisfactory procedure might be developed by using the rat as a test animal. Preliminary experiments in 1939 on a series of 440 rats convinced us that the rat may be employed for the bio-assay of the gastric secretory depressant activity of urine extracts (urogastrone) and duodenal mucosa extracts (enterogastrone).

One of the obstacles in employing the rat has been the difficulty in obtaining animals with empty stomachs. Because of the well-known habit of coprophagy, the stomach is found to be filled with ingesta even after withholding food for 40 hours. By encasing the rats in specially constructed jackets, Roe and Dyer (1) obtained animals with empty stomachs. We used Roe's jackets when studying gastric secretion in the rat but found the method impractical when assaying extracts on 20 or more animals at a time. Fasting the animals in specially constructed individual open-bottom cages was found very satisfactory. After 24 hours' fasting, only 1 to 3 animals out of every series of 20 used were found to have stomachs containing ingested matter. It is, therefore, advisable to fast 2 or 3 extra animals in order to keep the contemplated number of animals in an experiment intact.

The rat method of assay of gastric secretory depressants perhaps may be exemplified by our tests of potency of urine extracts. In our previous study (2) of inhibition of gastric secretion in dogs we found that extracts of urine depressed gastric secretion after a latent period of 30 to 45 minutes. This fact was utilized when assaying the urine extracts on rats. The animals are anaesthetized with nembutal, 35 mg. per kilogram body weight, and are fastened supine on rat boards. The stomach is exposed by an abdominal incision; animals with filled stomachs are discarded. Discarded animals are replaced by others found suitable, so that a total of 20 animals constitute the series. To 10

of the rats the urine extract is administered intravenously (ventral caudal or femoral vein), the other 10 receiving the same volume of saline. After an interval of 30 minutes the stomach is ligated at the pylorus, care being taken not to interfere with the blood supply. As Roe and Dyer found, and we have confirmed, no ligature is necessary at the cardiac end of the stomach. Extracts which depress markedly gastric secretion in the dog inhibit gastric secretion in the rat, while extracts ineffective in the dog are also ineffective in the rat. By allowing the gastric secretion to accumulate within the stomach for a period of exactly one hour after stomach ligation, a picture of marked contrast between the groups is attained (Fig. 1, 2). By means of



Figure 1 — Treated with urine extract; stomach only partially filled. A No. 20 hypodermic needle inserted through the navel, the gastric secretion is withdrawn every 30 minutes for an hour and a half. The difference in the

total volumes of juice secreted during this period by the 2 groups of rats is striking when a potent extract is used (Table I).

TABLE I

Urine Extract No. 423 i (Dose — 1 mg.)

Control ¹		Injected	
Rat No.	cc. for 90 min.	Rat No.	cc. for 90 min.
1	4.1	11	1.0
2	2.9	12	1.8
3	1.7	13	1.7
4	2.9	14	1.1
5	4.3	15	1.7
6	4.0	16	2.8
7	3.8	17	0.9
8	3.1	18	1.8
9	3.9	19	1.4
10	4.0	20	1.5

Control Series, avg., 3.5 cc.
Injected Series, avg., 1.6 cc.
Per cent Inhibition — 54.3.

In the procedure used originally both the test and control rats received repeated doses of histamine subcutaneously. It was believed that a standard secretory stimulus would be necessary to activate the rat's gastric glands. Histamine has been used for this reason in the assay method employing the pouch dog. However, later we (3) found that histamine is ineffective in the rat as a gastric secretory stimulant and that gastric secretion in this species is continuous and apparently spontaneous. This has since been confirmed by Komarov and coworkers (4). We further found that histamine did not modify in any demonstrable manner the depressant action of potent urine extracts on the spontaneous gastric secretion in the rat.

It was observed that varying the time interval between various steps of the procedure gave rise to different results. Consequently results are strictly comparable only when based on assays carried out under identical conditions. We have tested to date only extracts prepared from human urine, dog's urine, dog's intestinal mucosa and beef muscle, but probably the method will be found applicable to the study of other types of gastric secretory depressants as well.

We found that the degree of inhibition produced by a given extract is in proportion to the amount of extract employed (Table II). The method appears to have definite promise of being reliable, rapid and reproducible. We tentatively define a rat unit as that amount of urine extract (or other substance) which

TABLE II

Extract No.	Dose — mg. per rat	% Inhibition
423 a	2.0	34.7
	2.0	25.1
423 s	2.0	11.5
	1.0	3.2
423 i	1.0	54.3
	0.75	33.3
	0.5	24.1
423	1.0	48.0
	1.0	48.1
	0.5	33.0
	0.5	31.0
	0.5	36.0
	0.5	31.0

when given under the conditions described to a series of 10 or more rats produces 50 per cent inhibition of gastric secretion as compared with a like number of control rats studied simultaneously.



Figure 2 — Control: Note distended stomach.

REFERENCES

1. Roe, J. H. and Dyer, H. M.: Proc. Soc. Exper. Biol. Med., 41:603, 1939.
2. Friedman, M. H. F., Recknagel, R. O., Sandweiss, D. J. and Patterson, T. L.: Proc. Soc. Exper. Biol. Med., 41:509, 1939.
3. Friedman, M. H. F.: Proc. Soc. Exper. Biol. Med., 54:42, 1943.
4. Komarov, S. A., Shay, H., Rayport, M. and Fels, S. S.: Gastroenterol., 3:406, 1944.

The Role of the Coenzymes of the B Complex Vitamins and Amino Acids in Muscle Metabolism and Balanced Nutrition

By

SIMON L. RUSKIN, M.D.
NEW YORK, NEW YORK

THE evolution of nutrition from the field of folklore to an exact science is the result of three major independent advances chiefly of the last twenty years. Starting with initial studies in amino acids, interest jumped to the vitamins and now to the chemistry of muscle metabolism.

Through the interrelationship of the amino acids, the vitamins of the B complex and the adenylic acid system underlying muscle dynamics, we are now able to present a completed picture that gives a rationale to the jig saw elements of nutrition.

While Osborne and Mendel's famous experiments showed the amino acid basis of protein value in nutrition, Funk, Hart, Hopkins, McCollum, Steenbock and others branched off to explore the field of the "little things" that made nutrition either fail or go. Each developed as separate apparently independent fields. The failure to correlate amino acid research with vitamins of the B complex is perhaps responsible for much of the disappointment in vitamin B therapy.

The fact that the ultimate results of nutrition must be translated in terms of motion and growth led to studies primarily of growth. This was a natural path since growth could easily be observed and measured. The interpretation of nutrition in terms of calories was still a far cry from the understanding of nutrition in the dynamics of muscular contraction.

The work of Rose in demonstrating the essential nature of ten of the amino acids for growth gave a basis for dove-tailing the vitamins of the B complex, without which the essential amino acids were powerless to produce growth, thus establishing an intimate relationship between the amino acids and the vitamins.

Vital as these elements were in growth, they could not be separated from the functions of muscular contraction, for the B complex vitamins simultaneously participated in the hydrogen transfer in the breakdown of carbohydrate making available the energy for muscular contraction.

This intimate association between the B complex and the utilization of liberated energy by muscular contraction is bridged by adenylic acid.

We thus are able to present a unified picture of the dynamics of nutrition consisting of amino acids, B complex vitamins and the adenylic acid system represented by adenosine, mono-, di- and triphosphoric acid.

It is the object of this paper to show these relationships through the detailed study of these three basic elements and to carry over into the field of practical

nutrition the conclusions of this study. For this purpose, we will consider first the chemistry of muscular contraction, then passing to the mode of action of the B complex vitamins reach to the rôle of the amino acids.

The primary substance that needs to be considered in explaining muscle contraction is myosin. It occupies 75 per cent of the muscle volume. It is a practically soluble gel containing 80 per cent water. After excitation it has become significantly less soluble.

The contraction of muscle is in some way analogous to the contraction of all protein fibres in changed chemical environments.

The unit of striated muscle is a myofibril relatively loosely attached to others to make up a single muscle fibre. The myofibril itself is composed of chain-like molecules of myosin which may or may not be aggregated into a number of micelles. Along each fibre there is a regular alternation of more or less birefringent material, the more birefringent having the greater refractive index.

On contraction of the muscle under normal conditions there is a small diminution of total volume and a rapid evolution of heat. This change gradually disappears in relaxation, but a fresh supply of heat is given out and a number of very complicated chemical changes which may, but need not, involve oxidation, take place. The myosin molecules in the fibril are in the curled state similar to that of the well known keratin molecule. This is easily recognized developmentally where according to Weed each fibre is laid down originally separately from the others and develops striation which are shown by angular kinks, demonstrating that one portion (A) is less rigid than the other (I). The whole of the contraction takes part in the A region and even in isometric contraction the I region increases in length.

Thus the unit of striated muscle, the myofibril, is a continuous structure passing through many striations and carries in itself all the periodic properties of striated muscle. That is, it consists alternately of two portions differing principally in that one, the anisotropic portion (A) has a markedly stronger positive double refraction than the other usually referred to as the isotropic portion (I). These are in resting vertebrate muscle of about the same length, that is 1μ , the width of the fibril in different muscles varies from 0.5μ to 1.5μ . The isotropic and anisotropic portions of the fibrils keep remarkably closely in line with each other giving the striated appearance and leading to the hypo-

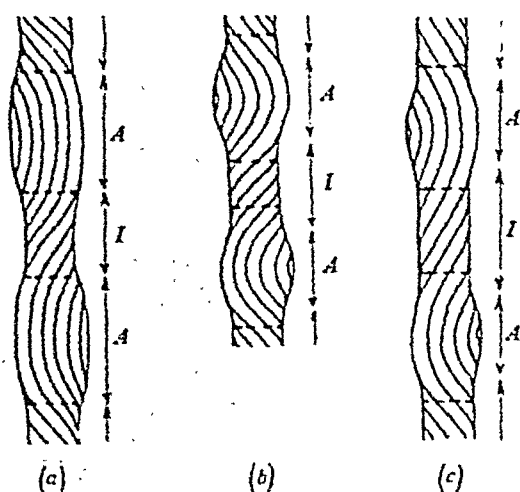


Figure 1—Molecular models of striated muscle fibril contraction (a) muscle relaxed, (b) isotonic contraction, (c) isometric contraction. The regions marked A and I correspond to the anisotropic and isotropic bands respectively. The marks --- across the molecular bundles indicate the division between the isotropic and anisotropic portions in the relaxed state.

—After Bernal.

thesis of a continuous membrane (Krause or Z membrane). Bernal feels "that the initial process of contraction was one of mechanical or electrical character rather like the release of a spring or the discharge of a condenser, while the recovery process involved chemical reactions taking place at definite and much slower rates." My own opinion is quite the reverse. I believe that the initial process of contraction is a chemical process, and the recovery is the result of electrical flow (electron flow). The reasons for this conclusion may briefly be stated as follows:

The disposition of the colloidal micellae gives the appearance of a double spiral to the anisotropic portions of the myofibril. As a result of the influence of the K ion, a colloidal change occurs leading to a contraction of the colloidal mass with a disturbance of the spiral structures possibly secondary to change in solubility of the myosin adenylate (adenosintriphosphatase). This may be considered pretty much the same as the collapse of spiral staircase. The rearrangement of such a structure would require a uniform type of force such as would be supplied by an electrical charge from a nerve impulse. One would then ask how would a spiral or helical structure arise from an electrical current.

For this mechanism to occur, we would have to accept a newer concept of electrical energy, that is, that electrons travel in helical paths rather than in straight lines. Thus the helical path of the electrons would tend to restore the helical structure of the micellae in the myofibril. This recognition of the helical character of electron flow, if accepted, would force us to revise much of our physiological conceptions, and opens up a better understanding of muscle action. It also provides a biologic background for a newer understanding of the physics of electrical charges.

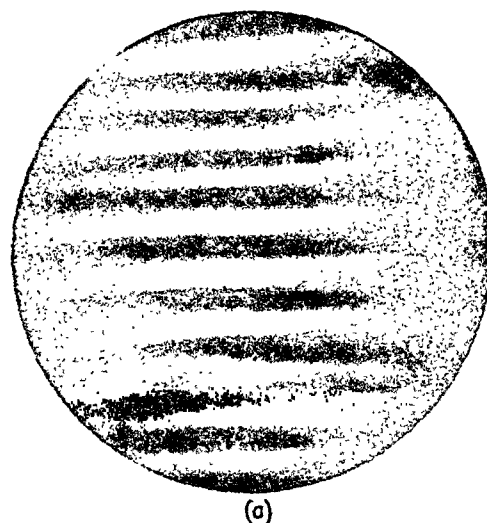
Thus there would be three phases in muscular action; one, under the influence of an initial electrical impulse, the inorganic ionic shift perhaps of the K ion; second, the organic protein shift; and third, the con-

tinued electronic flow restoring the micellae to the helical forms, and ready for the next cycle. A mechanism of this nature would also explain the speed of muscular reactions, and the production of the stage of relaxation.

In addition to the helical flow of electrons in the myofibril, there may be a second larger spiral flow embracing all of the muscle fibrils within the muscle sheath, thus accounting for uniformity of action.

When the nerve impulse reaches the myofibril originally, the adenosine triphosphoric protein compound under the influence of the Potassium ion shifts to adenosine diphosphoric and adenylic with a profound release of energy. This is the stage of contraction and inorganic phosphate is set free starting glycolysis. Under the influence of glycolysis, the adenylic acid and adenosine diphosphoric is built up to adenosine triphosphoric which the calcium ion restores to the original adenosine triphosphoric protein compound producing another release of energy. Under the influence of electron flow, the spiral structure is reformed. This is the stage of relaxation. The repetition of the cycle is now ready.

The role of calcium in this mechanism is also extremely interesting since I have shown in previous work that serum calcium is apparently bound to ascorbic acid, and the dissociation of the calcium ascorbate serves to activate through the calcium ion the protein enzyme adenosine triphosphatase while the ascorbate radical activates arginase, esterase, phosphatase, succinic dehydrogenase and cytochrome oxidase.



(a) Tobacco mosaic virus solution in tube showing reversed spiral arrangement (van Iterson). X80. Crossed micelles.

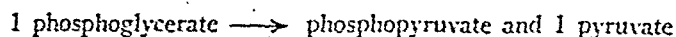
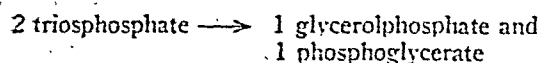
It is interesting that while Bernal observed that the micellar arrangement of muscle protein followed a typical spiral pattern he could propose no mechanism for its formation.

He did not, however, recognize the helical character of electronic flow which I propose as the underlying cause for this arrangement.

X-ray studies of muscle fibres seem to bear out this micellar arrangement in muscle fibre. This spiral coil arrangement is not limited to muscle fibres. Van Iterson

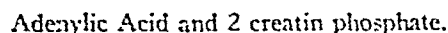
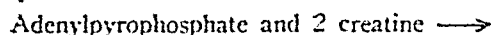
amounts suffice, provided that the extract has not been freed from adenylypyrophosphatase. In fact, the coenzyme function of the adenylic compounds as phosphate transporters is clear.

To set Cycle II in motion, it is not necessary to add pyruvic acid, for this can be formed from the triosephosphate.



In the reaction between phosphopyruvic acid and adenylic acid, energy as well as phosphate is transferred from one organic molecule to the other, for the synthesis of one gm. mol. of adenylypyrophosphate needs 24,000 gm. cal. of which 17,000 are provided by the hydrolysis of the two gm. mols. of phosphopyruvic, the rest coming from the heat of the surroundings. This cooling effect has actually been observed by Needham agreeing in amount with the calculated value.

Another reaction in which phosphate and energy pass between organic molecules was studied by Lohmann in muscle extract. The reversible reaction is described as follows:



Here the heat provided by hydrolysis of one molecule of adenylypyrophosphate is just about equivalent to that needed for synthesis of two molecules of creatine phosphate and the reaction is thermally neutral.

It is not frequent that a clinical application can follow closely the laboratory demonstration. In this case, the administration clinically of adenylic acid as the iron salt (Ironyl) is a brilliant demonstration of an almost immediate supply of muscle energy. The injection of 34 mg. of Ironyl containing 28 mg. of adenylic acid is followed by dramatic relief from fatigue and a sense of increased energy.

Strangely enough, the mechanics of increased energy are also affected by the adenylic nucleotide since it is followed by peripheral vascular dilatation and increased coronary flow. The sense of precordial distress observed in cases of coronary spasm is rapidly relieved by injection of Ironyl. So profound is this influence on the vascular mechanism, that injection into a vein may be followed by a marked drop in blood pressure and syncope. There is an initial increase in heart rate followed by slowing of the pulse. In cases of high blood pressure, there is a lowering of the diastolic level, and in low blood pressure, an elevation of the systolic. This remarkable stabilizing property of the adenylic nucleotide has not received adequate attention.

How the adenylic nucleotides perform their many and varied functions is perhaps most easily followed through its influence on the vitamins of the B complex.

To separate adenylic acid from thiamin, riboflavin

SCHEME I

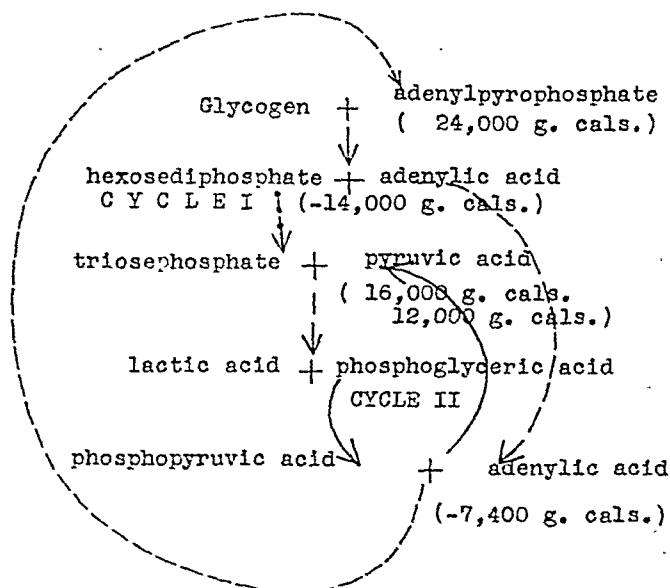


Figure 3—After Needham.

SCHEME II

1. Glycogen + $2H_3PO_4 \longrightarrow 2$ hexosemonophosphate
2. 2 hexosemonophosphate + adenylypyrophosphate \longrightarrow 2 hexosediphosphate + adenylic acid (+24,000 gm. cal.).
3. 2 hexosediphosphate \rightleftharpoons 4 triosephosphate (-28,000 gm. cal.).
4. 4 triosephosphate + 4 pyruvate \longrightarrow 4 phosphoglycerate + 4 lactate (+32,000 gm. cal. + c. 24,000 gm. cal.).
5. 4 phosphoglycerate \longrightarrow 4 phosphopyruvate (± 0 gm. cal.).
6. 2 phosphopyruvate + adenylic acid \longrightarrow 2 pyruvate + adenylypyrophosphate (-7,400 gm. cal.).
7. Adenylypyrophosphate + 2 creatine \longrightarrow 2 creatinephosphate + adenylic acid (+1,000 gm. cal.).
8. 2 phosphopyruvate + adenylic acid \longrightarrow 2 pyruvate + adenylypyrophosphate (-7,400 gm. cal.).

Figure 4—After Needham.

and niacinamide, and call the latter active agents, is the equivalent of separating the limbs from the body and calling them the active agents. Unless the adenylic is present to be the body for the B complex vitamins, there can be no activity since it is only through the adenylic nucleotide that the coenzyme which is the basis for the active enzyme does the work. There has not yet been demonstrated any physiologic function which either thiamine, riboflavin or niacinamide alone can perform. It is true that they are necessary for the formation in the body of the respiratory enzymes needed for carbohydrate utilization, but in themselves, they are rapidly excreted unless they can be converted to the coenzyme and then the enzyme. The following formulae show the coenzyme structures:

1. Cocarboxylase
2. Riboflavine phosphoric acid
3. Coenzyme I and II

A splendid schematic representation of the various

daily requirements as seen in Chart I, and knowing the daily expenditure of calories, we should be able to cal-

CHART I

PROTEIN REQUIREMENT FOR OPTIMAL NUTRITION

(National Research Council)

Individual	Daily Protein Requirement grams
Man (70 kg.)	70
Woman (56 kg.)	60
Pregnancy (Latter half)	85
Lactation	100
Children — Up to 12 years	
Under 1 year	3-4 (per kg.)
1-3 years	40
4-6 years	50
7-9 years	60
10-12 years	70
Children over 12 years	
Girls 13-15 years	80
16-20 years	75
Boys 13-15 years	85
16-20 years	100

culate the amount of carbohydrate required, and the amount of vitamin coenzymes needed. Such calculations could form a real basis for the determination of vitamin requirements. Such study is in progress and a report will soon be available.

The splendid studies of Block and Bolling, Rose, Melnick, Cameron, Emerson and Herbert have cast a great deal of light on the sources of correctly balanced amino acids for human nutrition.

Proteins containing all of the required amino acids in correct balance for human nutrition are considered 100 per cent biological. That is, they will support normal growth. One such protein is lactalbumin (Chart II). The absence of one or more of the essential amino acids reduce the biologic value of the protein. N. C. Rose has tabulated the amino acids as follows:

Indispensable or Essential	Dispensable or Non-Essential
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic Acid
Isoleucine	Glutamic Acid
Threonine	Hydroxyglutamic Acid
Methionine	Proline
Valine	Hydroxyproline
Arginine	Citrulline
	Cystine
	Tyrosine

Arginine can be synthesized by the animal organism, but not rapidly enough to meet demands of normal growth.

CHART II PROTEIN FOR NITROGEN EQUILIBRIUM IN DOGS

(Cowgill and Melnick)

Protein	Protein Minima for Nitrogen Equilibrium	Relative Biological Value
Lactalbumin	6.9	100
Serum protein	8.6	80
Casein	9.4	73
Gliadin	21.1	33

CHART III

COMPARISON OF VARIOUS EXCELLENT SOURCES OF DIETARY PROTEIN

(Melnick)

Criterion	Yeast Powder	Average Meat	Whole Eggs	Whole Milk	Defatted Soybean
Protein content (N x 6.25), %	46	19	13	3.5	50
Protein content, % total solids	49	63	50	37	54
Coefficient of digestibility of protein, %	75	98	100	100	86
Biological value of protein, %	74	72	94	85	77
Over-all nutritional value of protein, %	55	71	94	85	66
Over-all nutritional value of total solids in food as a source of protein, %	27	45	47	32	36
Essential amino acids of protein %					
Lysine	6.0	7.6	6.0	7.5	4.8
Isoleucine	3.4	3.4	5.3	4.4	4.0
Tryptophane	1.8	1.3	1.6	1.6	1.6
Threonine	5.0	3.7	4.9	4.6	4.0
Valine	4.4	3.4	4.4	4.5	4.5
Methionine	2.0	3.2	3.5	2.8	2.0
Histidine	2.8	2.1	2.4	2.5	1.8
Leucine	13.2	12.1	10.0	16.2	7.7
Arginine	4.3	7.2	7.0	4.3	5.3
Phenylalanine	4.1	4.5	5.6	5.7	5.7
Total	47.0	48.5	59.7	54.1	41.4

CHART IV APPROXIMATE PERCENTAGE OF AMINO ACIDS IN SOME PLANT PROTEINS, CALCULATED TO 16.0% NITROGEN

(Melnick)

	Cottonseed %	Linseed %	Peanut %	Soybean %	Yeast %
Arginine	7.4	6.2	9.9	5.8	4.3
Histidine	2.6	1.5	2.1	2.3	2.8
Lysine	2.7	2.5	3.0	5.4	6.0
Tyrosine	3.2	5.1	4.4	4.1	4.2
Tryptophane	1.3	1.9	1.0	1.5	1.4
Phenylalanine	6.8	5.6	5.4	5.3	4.1
Cystine	2.0	1.9	1.6	0.6-1.4	1.3
Methionine	1.6	3.0	0.9	1.8	2.0
Threonine	3.0	5.1	1.5	4.0	5.0
Leucine	14.0	5-10	10.0	8.0	13.0
Isoleucine	3-4	3-4	3-4	4.0	3-4
Valine	7.0	6.0	7.0	4-5	4-5
Glycine	5.3		5.6		

CHART V

CONTRIBUTION OF VARIOUS FOODSTUFFS
TO THE TOTAL CONSUMPTION OF
ESSENTIAL AMINO ACIDS

(Melnick)

	Dairy Prod- ucts %	Meats and Fish %	Eggs %	Beans and Nuts %	Cereals %
Protein	21	38	8	6	27
Arginine	17	46	11	6	20
Histidine	23	26	9	4	28
Lysine	27	50	8	5	10
Tyrosine	26	31	9	5	29
Tryptophane	26	37	10	5	20
Phenylalanine	22	33	8	6	31
Cystine	17	32	13	4	34
Methionine	18	40	10	3	29
Threonine	24	40	10	5	21
Leucine	22	33	11	3	31
Isoleucine	26	32	10	5	27
Valine	31	30	9	6	24

CHART VI

RECOMMENDED DAILY CONSUMPTION IN
GRAMS OF ESSENTIAL AMINO ACIDS

	Calculated gm. / day	According to Macy gm. / day	Based upon Average U. S. Diet gm. / day
Arginine	1.2	4.7	4.7
Histidine	2.4	1.6	2.0
Lysine	6.0	4.6	5.2
Tyrosine		3.9	3.9
Tryptophane	1.2	0.9	1.1
Phenylalanine	4.2	4.2	4.7
Cystine + Methionine	3.6	3.7	4.1
Threonine	3.6	3.2	3.6
Leucine	5.4	9.6	12.6
Isoleucine	3.0	3.1	3.7
Valine	4.2	3.2	3.9

Cystine and tyrosine may replace methionine and phenylalanine to a limited extent.

Melnick tabulates a comparison of various excellent sources of Dietary Protein as follows (Chart III):

A comparative study of vegetable, cereal and animal proteins reveals a marked difference in some of the essential amino acids so that diets adequate in caloric value may still lead to nutritional deficiencies.

If we study Chart IV, we observe the excellent proportions of animal proteins. However, when we compare it with Charts V, VI, VII, VIII, IX, X and XI, we observe a marked drop in lysine, arginine and histidine. Since these three amino acids are essential in formation of globin for haemoglobin, the inadequacy of plant proteins becomes obvious.

How serious such deficiency can become was manifested in the nutritional disturbances in Europe after World War I when after large shipments of cereals and grains, nutritional oedema was prevalent even

CHART VII

PERCENTAGE OF OPTIMAL DAILY RE-
QUIREMENT FOR EACH OF THE ESSENTIAL
AMINO ACIDS SUPPLIED BY 100 gm. PRO-
TEIN OBTAINED FROM EACH OF THE
SPECIFIED FOODS

(Melnick)

Amino Acid	Average Require- ment Calculated gm.	Supplied by 100 gm. Protein from:					
		Meat %	Milk %	White Flour %	"Enriched" Bread %	Corn %	Soybeans %
Arginine	3.5	210	125	110	110	115	165
Histidine	2.0	105	125	110	113	120	115
Lysine	5.2	145	140	40	55	40	105
Tyrosine	3.9	80	140	100	113	155	105
Tryptophane	1.1	110	175	90	120	55	145
Phenylalanine	4.4	100	130	125	115	105	125
Cystine + Methionine	3.8	110	105	110	110	130	80
Threonine	3.5	125	135	80	80	105	120
Leucine	0.1	135	180	130	120	240	90
Isoleucine	3.3	105	135	110	100	115	125
Valine	3.8	90	145	90	80	120	115

CHART VIII

COMPARISON OF THE ESSENTIAL AMINO
ACID CONTENT OF BEEF BLOOD HYDROLY-
SATE WITH THAT OF RECOGNIZED EXCEL-
LENT SOURCES OF DIETARY PROTEIN

(Melnick)

Amino Acid	% Beef Blood Hydrolysate					
	Meat Protein %	Whole Egg Protein %	Whole Milk Protein %	Yeast Protein %	Soybean Protein %	
Lysine	8.5	7.6	6.0	7.5	6.0	4.8
Isoleucine	0.5	3.4	5.3	4.4	3.4	4.0
Tryptophane	1.0	1.3	1.6	1.6	1.8	1.6
Threonine	6.8	3.7	4.9	4.6	5.0	4.0
Valine	11.0	3.4	4.4	4.5	4.4	4.5
Methionine	2.7	3.2	3.5	2.8	2.0	2.0
Histidine	4.3	2.1	2.4	2.5	2.8	1.8
Leucine	0.1	12.1	19.0	16.2	13.2	7.7
Arginine	4.3	7.2	7.0	4.3	4.3	5.3
Phenylalanine	6.9	4.5	5.6	5.7	4.1	5.7
Total	56.0	48.5	59.7	54.1	47.0	41.4

among those getting enough cereals to supply adequate caloric intake.

Nutritional oedema is a disturbance of water metabolism closely resembling nephrosis, particularly in regard to the hypoproteinemia.

In an earlier publication on the "Mechanism of Nephrosis" read before the Third International Pediatric Conference held in London, 1933, and reprinted in the Acta Paediatrica, I pointed out that not only does hypoproteinemia in general play a role, but also deficiencies in non protein nitrogen, particularly, nucleic acid and the nucleotides including adenylic acid. In the light of recent developments, this article may be well worth reviewing.

CHART IX

APPROXIMATE PERCENTAGE OF AMINO ACIDS IN SOME ANIMAL PROTEINS, CALCULATED TO 16.0% NITROGEN

(Melnick)

Amino Acid	Whole Human Milk	Whole Cow's Milk	Casein	Whole Egg	Whole Blood	Egg White
Arginine	5.0	4.3	4.1	4.2	4.2	5.8
Histidine	2.7	2.5	2.5	5.9	2.4	2.2
Lysine	7.2	7.5	6.9	8.0	6.0	6.5
Tyrosine	5.1	5.3	6.4	3.8	5.0	4.8
Tryptophane	1.9	1.6	1.5	1.5	1.6	1.6
Phenylalanine	5.9	5.7	5.2	6.2	5.6	5.5
Cystine	3.4	3.1	0.4	1.8	2.1	2.3
Methionine	2.0	2.8	3.5	1.5	4.0	4.4
Threonine	4.6	4.6	3.9	6.6	4.9	
Leucine	15.0	15.0	12.0	15-20	19.0	
Isoleucine	5.2	4.4	5.0	2.0	5.3	
Valine	5.5	5.0	7.0	5-6	4-5	
Glycine			0.5			3.3
Total	63.0	60.0	59.0	67.0	67.0	

CHART X

APPROXIMATE PERCENTAGE OF AMINO ACIDS IN SOME ANIMAL PROTEINS, CALCULATED TO 16.0% NITROGEN

(Melnick)

Amino Acid	Meat	Egg	Grain
Arginine	7.1	5.6	7.6
Histidine	2.2	1.9	1.0
Lysine	8.1	6.8	4.3
Tyrosine	3.1	4.0	0.2
Tryptophane	1.2	1.3	0.0
Phenylalanine	4-5	4-5	1.8
Cystine	1.1	1.2	0.1
Methionine	3.3	3.4	0.8
Threonine	4.3	4.4	1.5
Leucine	12.0		4.0
Isoleucine	3.4		1.0
Valine	3-4		2.0
Glycine	5.0		23.6

CHART XI

APPROXIMATE PERCENTAGE OF AMINO ACIDS IN SOME PLANT PROTEINS, CALCULATED TO 16.0% NITROGEN

Amino Acid	Whole Grain	Grain	Whole Grains	Wheat Protein	Corn Protein	Wheat Protein	Endosperm	Endosperm
Arginine	4.0	3.0	6.0	3.1	3.9			
Histidine	2.4	1-2	2.7	2.5	1.7	2.2		
Lysine	2.5	2.7	5.8	5.5	1.1	1.0		
Tyrosine	6.1	3.8	4.9	3.8	6.2	3.8		
Tryptophane	0.6	1.0	1.3	1.0	0.6	1.0		
Phenylalanine	4.5	5.7	5.6	4.2	6.6	5.5		
Cystine	1.1	1.3	1.2	0.6	1.2	1.8		
Methionine	4.0	3.0	2.3	2.0	5.5	3.0		
Threonine	5.6	3.3	4.4	3.8	4.0	2.6		
Leucine	22.0	13.0	16.0	7.0	25.0	12.0		
Isoleucine	3-4	4.0	3.0	5.0	4.0			
Valine	5.0	3-4	6.0	3-5	5.0	3.0		
Glycine					4.0	8.0		

CHART XII

COMPARISON OF THE ESSENTIAL AMINO ACID CONTENT OF BEEF BLOOD HYDROLYSATE WITH THAT OF PROTEINS OF HIGH NUTRITIVE QUALITY FOR PURPOSES OF PARENTERAL PROTEIN ALIMENTATION

(Melnick)

Amino Acid	Recommended Intake		gm./70 gm. Hydrolyzed Protein									
	Based upon Rose's values (20)	Based upon Block's values (41)	Average	Beef Blood	Hydrolysate	Meat Protein	Whole Egg Protein	Milk Protein	Yeast Protein	Boiled Soybean Protein		
Arginine	1.2	4.8	3.0	3.0	5.0	4.9	3.0	3.0	3.0	3.7		
Histidine	2.4	1.8	2.1	3.0	1.5	1.7	1.8	2.0	1.3	1.5		
Isoleucine	3.0	3.3	3.2	0.4	2.4	3.7	3.1	2.4	2.8			
Leucine	5.4	10.7	8.1	6.4	8.5	13.3	11.3	9.2	5.4			
Lysine	6.0	5.1	5.6	6.0	5.3	4.2	5.3	4.2	3.4			
Methionine	3.6	4.0	3.8	1.9	2.2	2.5	2.0	1.4	1.4			
Phenylalanine	4.2	4.3	4.3	4.8	3.2	3.9	4.0	2.9	4.0			
Threonine	3.6	3.4	3.5	4.8	2.6	3.4	3.2	3.5	2.8			
Tryptophane	1.2	1.1	1.2	0.7	0.9	1.1	1.1	1.3	1.1			
Valine	4.2	4.2	4.2	8.3	2.4	3.1	3.2	3.1	3.2			

The basic factor underlying generalized oedema is urea formation and clearance. The diuretic effect of urea is only too well known. One of the major urea cycles is the formation of urea from arginine, through ornithine and citrulline. The urea thus formed removes water from the tissues. A cereal diet low in arginine would produce but little urea with resultant water retention.

Another factor that has been inadequately reckoned with is the non protein nitrogen representing for the major part nucleic acid. Every cell that is consumed also supplies nucleic acid. This is inevitably true of all animal and plant protein. The nucleic acid is made up of four nucleotides, adenylic acid, guanylic acid, thymilic (or uridylic in plants) and cytidilic acids. These nucleotides constitute the major non protein nitrogen elements. Two nucleotides are purines, adenylic and guanylic and two pyrimidines, thymilic and cytidilic. All have the basic pyrimidine structure attached to a ribose and phosphoric acid radical. The pyrimidine nucleus, when it is split, usually under the catalytic influence of iron or iodine yield urea, CO₂ and pyruvic acid. Thus a rich supply of urea comes from the nucleotides. I was able to demonstrate clinically, in 1933, that the severe oedema of nephrosis could be promptly relieved by oral administration of six to nine grams of nucleic acid, and I have demonstrated that nasal congestion and allergic states, as well as generalized fluid retention is very favorably influenced by administration of non protein nitrogen in the form of nucleic acid.

It therefore behooves us, in considering balanced nutrition, to provide adequate amounts of arginine, histidine, lysine and tryptophane.

Vice President Wallace, in an address to the Ameri-

CHART XIII
PERCENTAGE COMPOSITION OF SOME PLANT PROTEINS CALCULATED TO 16.0% OF NITROGEN

(Melnick)

	Whole Corn	Corn Gluten	Corn Germ	Corn Albumins	Wheat Gluten	Wheat Germ	Yeast	Soybean
Arginine	4.0	3.1	6.8	5.4	3.9	6.0	4.3	5.8
Histidine	2.4	1.7	2.7	6.7	2.2	2.5	2.8	2.3
Lysine	2.5	1.1	5.8	low	1.9	5.5	6.4	5.4
Tyrosine	6.1	6.2	4.9	3.8	3.8	3.8	4.2	4.3
Tryptophane	0.7	0.6	1.3	0.7	0.8	1.0	1.4	1.5
Phenylalanine	4.5		5.6	1.7	5.5	4.2	4.1	5.4
Cystine	1.1	1.2	1.2	0.5	1.9	0.6	1.3	1.0
Methionine		5.5	2.6		3.0	2.0		2.0
Threonine	3.6	4.0	4.4	3.9	2.7	3.8	5.0	4.0
Leucine	21.5	2.4	24.7	3.7	16.3	3.1	11.3	4.1
Isoleucine	3.6	0.3	4.9	0.3	3.7	0.4	1.3	0.4
Valine	4.6	0.7	4.6	1.4	5.8	1.2	2.5	3.4
Sulfur	1.7	1.5	1.0	0.9	1.1		0.9	1.1

CHART XIV
EVALUATION OF BEEF BLOOD HYDROLYSATE AS A SOURCE OF ESSENTIAL AMINO ACIDS FOR DIETARY SUPPLEMENTATION

(Melnick)

Criterion	R A T I N G					
	1	2	3	4	5	6
Total quantity of essential amino acids furnished	Whole egg Protein	Beef blood Hydrolysate	Whole milk Protein	Yeast Protein	Meat Protein	Soybean Protein
Furnishing essential amino acids most likely to be deficient in diet	Beef blood Hydrolysate	Whole milk or whole egg Protein	Meat Protein	Yeast Protein	Meat Protein	Soybean Protein
Furnishing essential amino acids less likely to be deficient in diet	Whole egg Protein	Whole milk Protein	Meat Protein	Yeast Protein	Beef blood Hydrolysate	Soybean Protein

can Dietetic Association, pointed out that while we are in a position to supply the rest of the world with cereals and grains, it is quite a different matter as far as animal proteins are concerned. The conversion of plant proteins to animal proteins represents a costly conversion. It takes 7 pounds of corn to get 1 pound of pork with an energy loss of 84 per cent. The farmer is thus in a constant dilemma as to whether or not he is doing the traditional deal of buying eggs four for a nickel and selling them five for four cents. While this knotty problem is bedeviling the economics of the farmer, we must find a means of balancing the nutritional deficiencies of cereals and grains.

Fortunately, such possibilities exist in nature through the provision of yeast protein. Intermediate as they are in the biologic scale of life, they provide higher yields of those essential amino acids that are low in plant proteins and cereals. A glance at Chart VIII will show that yeast supplies 6 per cent lysine as against 6.8 per cent of fish and 1.1 per cent of corn and 1.9 per cent of wheat. Yeast also supplies 4.3 per cent of arginine as opposed to 3 per cent of wheat.

A study of the tables show the various amino acid deficiencies in the different foods as well as the daily and annual requirements of each. It is evident that supplements of high biologic value would go far to-

word correcting the deficiency of essential amino acids particularly in the absence of meat and dairy products. One of the large and readily available sources of such protein supplement is found in yeast.

While the digestibility of whole yeast is markedly reduced by the resistance of the cell wall to intestinal hydrolysis, this untoward factor may be overcome partly by plasmolysis of the yeast cell but far more effectively by creating enzymatically a complete protein hydrolysate of the yeast yielding the free amino acids and polypeptides. The speed of absorption of amino acids and polypeptides from the gastro-intestinal tract makes it ideally suitable as a nutritional supplement.

One of the outstanding developments in the field of yeast culture has been the development of a yeast strain that is high in protein value. Thus a rich enzymatic protein hydrolysate of yeast has become available in large quantities, sufficient to be a factor of international scope particularly for feeding of liberated countries.

An evaluation of food proteins for dietary supplementation places yeast high in the group of preferred sources (Chart XI).

How important such supplements are can be best observed in the nutrition of the aged. For them, meats and eggs are usually difficult to digest. With loss of teeth for mastication and diminishing gastric acidity

for hydrolysis, a cereal and grain diet automatically follows. A reduced intake of lysine, arginine, histidine and tryptophane is almost inevitable. A protein hydrolysate is an essential dietary supplement. These patients fed synthetic vitamins do not have the amino acids to form the respiratory enzymes, nor do they have the adenylic to form the coenzymes. Synthetic vitamin supplements in most instances represent sheer waste.

Unfortunately protein hydrolysates for oral use have been vile tasting, particularly casein or beef blood hydrolysates. In yeast hydrolysates we have however a much more palatable result.

A further development in this field has resulted from the reaction of whole yeast B complex coenzymes and yeast protein hydrolysate fortified with adenylic acid and a source of phosphoric acid such as glycerophosphoglyceric acid. By this procedure free thiamin is phosphorylated to cocarboxylase and riboflavin to riboflavin phosphoric acid. Nicotinamide may be added to form with the adenylic coenzyme I and II. In this manner there has been obtained an amino acid vitamin B complex coenzyme preparation ready for biologic reactions not dependent upon the chance availability of the necessary factors.

For the aged and infants, it represents an almost ideal nutritional supplement that is quite palatable, and for the patient needing vitamin supplements, there is a reasonable assurance of biologic activity.

Analyses of the yeast protein hydrolysate gave the following results:

AMINO ACIDS CALCULATED ON 16% NITROGEN BASIS

	Primary Dried Yeast	Meat	Cow's Milk
Arginine	4.3%	7.1%	4.3%
Histidine	2.8	2.2	2.5
Lysine	6.0	9.1	7.5
Tyrosine	4.2	3.1	5.3
Tryptophane	1.4	1.2	1.6
Phenylalanine	4.1	4-5	5.7
Cystine	1.3	1.1	1.1
Methionine	2.0	3.3	2.8
Threonine	5.0	4.3	4.6
Leucine	13.0	12.0	15.0
Isoleucine	3-4	3.4	4.4
Valine	4-5	3-4	5.0
Glycine	5.0	5.0	—

In considering protein hydrolysates, it is important to know what nutritional objective is desired. If total sustenance is required and no other sources of nitrogen are available, the hydrolysate should be made of a protein that is one hundred per cent biological, that is, it contains an adequate amount of all the amino acids necessary for tissue growth.

Protein formation follows the all or nothing law. If all the essential amino acids are not available, no protein will be formed. If all of the amino acids are present, but the percentage of some is low, a large amount of the substance will be necessary to form the small amount of tissue protein. Thus a casein hydrolysate

must be fed 15% to 18% of the diet to attain maintenance. Its approximate biologic value is 74 per cent.

On the other hand, lactalbumen or egg has a biologic value of one hundred per cent. It is apparent that nature intended to provide the where-with-all for total growth in these two proteins, and a hydrolysate of either should be theoretically ideal.

There are however, practical difficulties in the preparation of hydrolysates since an acid or alkali hydrolysis is associated with the destruction of either tryptophane, cystine or methionine, depending on the technique followed. Thus the ideal properties are lost. An enzymatic hydrolysis offers the best opportunity for retaining the full biologic value and by a technique to be described later, I have succeeded in hydrolysing jointly yeast and lactalbumin. This gives us a practical, close to biological hydrolysate, and for the maintenance of growth, is a close approximation to the ideal.

However, we must not lose sight of the fact that various tissue proteins are quite differently constituted in their ratio of amino acids. Thus it should not be expected that beef blood protein would supply other tissue proteins with a complete source; in fact, we find that beef blood hydrolysate is not one hundred per cent biological, and will not maintain complete nitrogen balance. From this angle, a meat hydrolysate should offer a better source for tissue protein growth, and from the practical angle, I believe this will be experimentally demonstrated. The economics of meat hydrolysate is however not too good, since the cost of the hydrolysate is far above that of meat, and, from the angle of national economy, makes scarcer an already scarce food source.

Earlier in this paper, I pointed out that nutrition must be studied, not only from the angle of growth, but also of energy. Our growth observations are quite simple. If the animal is maintained on a hydrolysate and loses weight and shows changes in its fur, it may be readily noted, whereas if an animal is maintained on a one hundred per cent biological diet, good growth will occur, but its energy and work capacity are not recorded.

For humans, however, the growth factor is, as a rule, less frequently a matter of concern than the energy factors. Fortunately, they are not kept wholly on a hydrolysate ration, and, at best, it is only a supplement. Clinically therefore, hydrolysates should not be looked upon for total nitrogen balance or whether it will keep a dog at full growth. It is to be viewed rather as a method of correcting specific defects. As an example, one could take a lysine deficient diet of a patient kept on a cereal and grain diet, and through a yeast protein hydrolysate elevate the lysine intake. Similarly a histidine deficient diet could be corrected by beef blood or meat hydrolysate.

The adult human is more concerned with energy requirements because outside of stark starvation, he is able to secure enough biologic protein for growth, and nature apparently gives growth and tissue replacement, first call on the amino acids. The energy requirements of the amino acids are primarily that for

the protein portion of body enzyme systems. The enzymes could be looked upon as the fluid tissues of the body. They are protein in the same sense as connective tissue, cartilage, bone, blood, organs or muscle. In fact, myosin, the muscle protein, I have previously stated is considered an enzyme, adenosinetriphosphatase.

We can therefore see that if we are looking to the amino acids for energy, we must look, not for tissue growth, but for enzyme sources. We cannot therefore take a hydrolysate for nitrogen balance and be assured of a source of enzyme protein. Conversely, a source of enzyme protein will not necessarily maintain nitrogen balance.

In this investigation, the primary objective is the study of the energy factors in nutrition. Just as the study of amino acids led to the discovery of vitamins, so the study of the vitamins led us back through the respiratory enzymes to the amino acids. In the study of the vitamins, yeast has played a dominant role since in the yeast we found a plentiful source of all of the B complex factors that control the energy metabolism of the body. From yeast, these vitamin factors have been successively isolated. Now in the same sense, we return to yeast for the amino acids, since they are precisely the amino acids with which the vitamin factors are normally bound. An enzymatic hydrolysate of yeast provides the ideal source for enzyme amino acids. It may not keep a dog in nitrogen balance, but it will provide the amino acids for respiratory enzyme formation, that is, for successful vitamin therapy.

Clinically, a patient living on a high alcohol, high carbohydrate diet, may be given adequate doses of thiamin, but be unable to make carboxylase for lack of adequate amino acid supply. This patient would get a complete supplement from a yeast hydrolysate. Similarly, a patient with gastric disturbance subsisting on a mush diet, will be low in lysine and would be corrected by a yeast hydrolysate. On the other hand, a patient with anemia would do well with a beef blood or meat hydrolysate. A combination of yeast hydrolysate and meat hydrolysate also offers special value in specific preparations.

Hydrolysates therefore, are really specific agents and should be selected for particular clinical conditions. For the correct administration of the B complex vitamin factors, the yeast protein hydrolysate must be considered as closest to ideal, since the respiratory enzymes occur in yeast as a complete biologic system. The technique of preparing the coenzymes of the B complex factors with the amino acids of the yeast protein hydrolysate, brings the B complex to a biologically active state in which it may be administered with confidence that the nutritional deficiency will be adequately corrected. The administration of synthetic B complex factors alone leaves too wide a gap between administration and biologic usefulness.

The vitamins, particularly the B complex group, play a very important role in our civilization today. Despite the drawbacks of uncertainty, and perhaps

lower percentage of utility in synthetic vitamins, the general average of clinical improvement is sufficiently great to convince the physician and patient of their usefulness. Statements that the vitamins are over exploited, and efforts made to restrict their administration would move nutrition away from the optimum rather than to it. Advancing our knowledge of the mode of action of the B complex vitamins through the study of the coenzymes and their specific usefulness will do more for the health and energy of the nation than withdrawing from the valuable discoveries already made in the vitamin field. The situation calls for forward vision rather than withdrawal.

The increased knowledge of the hydrolysates likewise opens up an enormous source of food supplies, not only for correcting injudicious or inadequate diets at home, but as a beneficent contribution to the food problems abroad. In yeast, nature has placed at our command the remarkable potential of converting, in a matter of hours, large amounts of inorganic nitrogen to protein nitrogen ready to be utilized by man or animal.

The great strides in yeast genetics have made possible strains of high protein content suitable through enzymatic hydrolysis as a high grade food supply.

CHART XV
APPROXIMATE AMINO ACIDS IN SOME
PLANT AND ANIMAL PROTEINS
(All Calculated to 16.0 per cent of Nitrogen)

Amino Acid	Yeast Max. %	Yeast Min. %	Average %	Yeast (10) %	Yeast (11, 12) %	Meat (3, 13) %	Casein (3) %	White Flour (3, 4) %	Corn Gluten (3) %	Polished Rice (14) %
Arginine	5.3	3.1	4.3	3.1	5.4	7.7	4.1	3.9	3.1	7.2
Histidine	3.1	2.3	2.8	3.3	3.1	2.9	2.5	2.2	1.6	1.5
Lysine	8.1	6.7	7.5	7.1	9.8	7.2	7.5	1.9	0.8	3.2
Tyrosine	3.7	3.4	3.6	3.8	6.0	3.4	6.4	3.8	6.7	5.6
Tryptophane	1.5	1.2	1.3	1.2	1.5	1.3	1.2	1.3	0.7	1.3
Phenylalanine	4.6	2.9	4.1	4.5	4.9	5.2	5.5	6.4	6.7	6.7
Cystine	1.1	0.9	1.0	1.1	2.3	1.3	0.4	1.9	1.1	1.4
Methionine	2.8	2.6	2.7	2.7	3.3	3.5	3.0	4.0	3.4	3.4
Threonine	6.0	5.1	5.5	5.5	5.4	3.9	2.7	4.1	4.1	4.1
Leucine	8.5	6.1	7.4	7.3	7.3	7.7	12.1	5.8	24.0	9.0
Isoleucine	6.2	5.5	5.9	6.0	5.8	5.2	6.5	3.3	5.0	5.3
Valine	5.9	4.6	5.0	5.3	5.7	5.7	7.0	3.6	5.0	6.3

CONCLUSION

1. The system of amino acids and coenzymes of the B Complex is necessary for the formation of the respiratory enzymes on which we depend for energy and growth.
2. The synthetic vitamins represent only one element of this system and alone are biologically inactive.
3. Precisely those patients who need vitamins are the ones most likely to be lacking the amino acids and adenylic acid necessary for the formation of the coenzymes.

REFERENCES

- Adlersberg, D. and Hauser, T.: Special Diets Under Rationing. *J. Am. Dietet. Assoc.*, Vol. 19, August 1943.
- Beach, E. F., Munks, B., Robinson, A. and Macy, I. G.: Dietary Evaluation of Animal Proteins from Their Amino Acid Contents. *J. Am. Dietet. Assoc.*, Vol. 19, August 1943.
- Bernal, J. D.: A Speculation on Muscle. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Block, R. J. and Bolling, D.: Nutritional Opportunities with Amino Acids. *J. Am. Dietet. Assoc.*, Vol. 20, September 1943.
- Cannon, P. R.: Protein Metabolism and Acquired Immunity. *J. Am. Dietet. Assoc.*, Vol. 20, February 1944.
- Dixon, M.: Respiratory Carriers. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Green, D. E.: Reconstruction of the Chemical Events in Living Cells. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Krebs, H. A.: Intermediary Hydrogen-Transport in Biological Oxidations. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Lloyd, D. J.: Recent Developments in Our Knowledge of the Protein Molecule. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Melnick, D.: Protein in Human Nutrition. Wallerstein Communications; Evaluation of a Protein Hydrolysate as a Source of The Essential Amino Acids for the Human. *J. Am. Dietet. Assoc.*, November 1943; The Essential Amino Acids in Human Nutrition. *J. Am. Dietet. Assoc.*, Vol. 19, pp. 685-92, 1943.
- Moore, S.: Recent Advances in Protein Chemistry. Wallerstein Communications.
- Needham, D. M.: Chemical Cycles in Muscle Contraction. Cambridge University Press, 1939.
- Peters, R. A.: Proteins and Cell-Organization. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Rose, W. C.: *Physiol. Rev.*, 18:109, 1938.
- Ruskin, S. L. and Katz, E.: Therapeutic Action of Nucleotides; Treat. of Whole Blood Picture with Ferrous Adenylate. *An. Int. Med.*, 9, 11, 36, 1549, 1560, May, 1936.
- Stamberg, O. E. and McBain, J. W.: The Protein Fractions. Wallerstein Communications.
- Potter, V. R.: The Role of Vitamins in Energy Transformations. *J. Am. Dietet. Assoc.*, Vol. 19, No. 7, July 1943.
- Ruskin, S. L.: Studies on Parallel Action of Vitamin C and Calcium. *Am. J. Dig. Dis.*, 5:408, 1938; Studies in Calcium Metabolism: Further Contribution to Comparative Studies of Physico-Chemical Properties of Gluconate and Cevitamate of Calcium and of Vitamin C. *Ibid.*, 5:676, 1938; Mechanisms of Nephrosis in Sinusitis in Children. *Acta Paediatrica*, 16, 249, 274, 1933; Nucleic Acid and Nucleotide Therapy in Nasal Diseases: Contributions to Study of Chemical Aspects of Nasal Diseases. *Arch. Otol.*, 22:172, Aug., 1935; Influence of Vitamin C on the Antihistaminic Action of Various Drugs. *Arch. Otol.*, 36:853-873, Dec. 1942; Adenylic Acid in the Treatment of Agranulocytosis and Mucous Membrane Lesions. *Am. J. Dig. Dis.*; The Therapeutic Use of the Amino Acid. Histidine in Allergy and Shock. "Histidine as a Factor in Histamine Epinephrine Balance." *J. Dig. Dis.*, Vol. 12, No. 7, July 1943; High Dosage Vitamin C in Allergy. *J. Dig. Dis.*, Vol. 12, No. 9, Sept. 1945.
- Ruskin, S. L. and Jonnard, R.: Etudes Physico-Chim. Comparat du Gluconate, du Sel de Calcium et de la Vitamine C. *Compt. Rend. de Biol.*, 28:266-268, 1938.
- Von Szent-Gyorgi, A.: Oxidation and Fermentation. Perspectives in Biochemistry. Cambridge University Press, 1939.
- Wright, S.: Wright Applied Physiology, p. 574. Oxford University Press, 1941.
- Weed, Z.: *Zellforsch.*, 1936, 25, 516.
- Van Iterson: *Proc. Kon. Acad. Wet. Amsterdam*, 1934, 37, 367.
- Bawden, et al.: *Nature*, London, 1936, 138, 1051.
- Asbury: *Nature*, London, 1935, 135, 765.
- Block, Richard J. and Bolling, Diana: The Amino Acids Yielded by Various Yeasts after Hydrolysis of the Fat-Free Material. A Comparative Investigation. *Arch. Biochem.*, Vol. 7, No. 2, pp. 313-321, July, 1945.

Book Reviews

Nutrition and Chemical Growth in Childhood, Vol. II, Original Data. By Icie G. Macy, Ph. D., Sc. D., pp. 1017 (\$10.00). Springfield, Illinois, Charles C. Thomas, 1946.

The previous volume (I) was an evaluation, containing the methods and techniques used in these studies and presented average data for children. The present volume (II) contains all the facts and figures—the medical histories, pictures of the subjects, chemical analyses of foods, urine and feces for consecutive balance periods over months for the same group of children and at different age levels for some individuals; anthropometric measurements; hematochemical

determinations; actual size reproductions of roentgenograms; medical and dental examinations; basal metabolic determinations and psychometric evaluations. This volume, which reflects credit on the author's ideals and the publisher's courage, is an exhaustive and profusely illustrated text of 1017 pages, and admittedly presents for the first time any truly comprehensive and coordinated study on the nutrition and chemical growth in childhood. The facts presented required many years of work and these facts form a valuable reference book for nutritionists and indeed, all clinicians. We shall await with interest the appearance of Volume III which will contain an integrated analysis and application of the data obtained.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
WM. D. BEAMER
IVAN BENNETT
J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

*With the Armed Forces.

CLINICAL MEDICINE

LIVER AND GALLBLADDER

SKELTON, M. O.: *The relation between congenital obliteration of bile ducts and icterus gravis neonatorum.* (Brit. Med. J., p. 914, Dec. 29, 1945).

Icterus gravis neonatorum and congenital obliteration of the bile ducts are two conditions causing jaundice in the new born. In numerous instances the clinical signs are very similar so that differentiation between the two may be difficult.

In children biliary obstruction may be due to blockage of one of the larger ducts with inspissated bile or to conversion of the duct walls into fibrous cords.

Biliary thrombi in icterus gravis probably are composed of necrotic or damaged cells from livers which already have suffered damage. Swollen epithelial cells of the ducts may also produce the blockage. Hepatic cirrhosis similar to that noted in congenital obliteration may be due to biliary stasis in obstruction of long standing. — F. E. St George.

THERAPEUTICS

BARCLAY, J. A. AND COOKE, W. T.: *Hepatorenal syndrome treated with choline chloride.* (Lancet, p. 458, Oct. 13, 1945).

The case is described of a patient who received several barbituric acid derivatives because of an anxiety state with depression. Ten days after beginning the barbiturates the patient became unconscious but was revived by picrotoxin. He passed bloody stool and vomited repeatedly but was anuric and experienced considerable abdominal pain. Jaundice developed and hiccupping and the vomiting continued. Intravenous saline and dextrose did not relieve the anuria. Choline was given the patient and improvement was soon noted. Methionine was later included also. The authors conclude that the hepatitis (perhaps aggravated by a previous liver injury in childhood), and the renal failure were probably due to barbiturate poisoning. — F. E. St. George.

McELIN, T. W. AND HORTON, B. T.: *Clinical observations on the use of benadryl: a new antihistamine substance.* (Proc. Staff Meet. Mayo Clinic, v. 120, p. 417, Nov. 14, 1945).

Benadryl (beta dimethylaminoethyl benzhydryl ether

hydrochloride) has the distinct property of preventing some of the pharmacological effects of histamine. The drug has three significant actions. It alleviates (1) the bronchial constriction caused by histamine or occurring in anaphylactic shock; (2) the vasodepressor effects of histamine and (3) the spasm of smooth muscle produced by histamine. Pharmacological studies suggest that the antispasmodic activity has three components: (1) an antihistamine action; (2) an antispasmodic action (antibarium chloride effect) and (3) an atropine-like effect (antiacetylcholine action). Among other clinical studies, the authors found that benadryl administered intravenously depressed the gastric response to intravenous histamine in the majority of cases. They feel that, if their preliminary observations can be substantiated, a new approach to the control of gastric acidity may become possible. — E. J. Tallant.

SURGERY

WAUGH, J. M. AND FAHLUND, T. R.: *Total gastrectomy.* (Surg. Clin. N. Amer., v. 25, p. 903, 1945).

From 1917 to 1943 there were performed 77 total gastrectomies in the Mayo Clinic, with an overall surgical mortality of 44 per cent. The mortality rate was higher in the 33 cases operated on prior to 1940 than in the 44 cases operated on from 1940 to 1943 inclusive (60.6 per cent compared with 3.18 per cent).

Several factors are listed as contributing to this dramatic decline in the operative mortality rate. Among these are improved post operative care, early recognition of post operative complications, the advent of chemotherapy and the additional experience gained by the surgeons from their earlier failures. Post operative survival has been good. Of the patients gastrectomized for cancer more than half have survived two or more years. Two patients who had total gastrectomies performed for benign gastric lesions are still alive 6 and 8 years later. — H. Stilyung.

COUNSELLER, V. S., WAUGH, J. M. AND CLAGETT, O. T.: *Report of surgery of the stomach and duodenum for 1944.* (Proc. Staff Meet. Mayo Clinic, v. 21, p. 17, Jan. 9, 1946).

During 1944, there was a hospital mortality rate of 4% in patients having operations on the stomach and duodenum. Forty-six per cent of the patients seen at

the Mayo Clinic who had a gastric ulcer were treated surgically, as compared to 60% for the preceding 5 years. This lowered rate was due to the fact that the patients were unable to afford the time required for surgery due to the press of war work and the inability to find substitutes in their work. The authors feel that all gastric ulcers should be treated surgically, except those in whom the operative risk outweighs the chance of a malignant lesion. They feel that it is impossible to definitely state that a gastric lesion is benign and that the chance of a malignant lesion being present is more than ten times the risk of partial gastrectomy. There was a mortality of 1.3% for operations on the stomach. Of 298 cases of malignancy of the stomach seen (288 carcinoma, 10 sarcoma) 60% were operable. Resection was performed in 60% and palliative procedures in 40% of those operated upon. Due to early diagnosis, 36% of all gastric malignancies seen underwent resection, one of eight resections being a total gastrectomy. There was a mortality rate of 5.3% for partial gastrectomy and 47.6% for total gastrectomy. The authors feel, in view of the rarity of malignancy in the first portion of the duodenum that the management of duodenal ulcer is a medical problem unless complications, such as hemorrhage, perforation, obstruction or intractability, intervene. Operation was performed upon 12% of the duodenal ulcers seen, 63% were partial gastrectomies with a mortality of 1% and 37% were gastro-enterostomies with a mortality of 1.5%. Partial gastrectomy was chosen for hemorrhagic ulcers and ulcers seen in young persons with an abnormally high gastric acidity, while gastro-enterostomy was chosen in the treatment of elderly patients presenting obstruction. — D. J. Tallant.

CLAGETT, O. T.: *Transthoracic resection of lesions of the lower portion of the esophagus and the cardia of the stomach.* (Proc. Staff Meet. Mayo Clinic, v. 20, p. 497, Dec. 26, 1945).

The author recommends the transthoracic approach as the procedure of choice for operation upon lesions of the lower portion of the esophagus and cardia of the stomach. He sees no reason for an abdominal operation to determine the operability of a carcinoma of the cardia before proceeding with transthoracic operation. He claims that there is no more risk to primary transthoracic exploration of the lesion than there is to abdominal exploration and operability can be determined as accurately. If the patient's condition is sufficiently good to consider transthoracic resection at all, it can be done without preliminary jejunostomy. The author feels that it is impossible to improve the patient's condition by jejunostomy sufficiently to justify the delay in removing the lesion itself. — E. J. Tallant.

EXPERIMENTAL MEDICINE

PATHOLOGY

GRAY, R. E., GROSSMAN, M. I. AND ROBINSON, H. E.: *Failure of intestinal extracts to prevent chick gizzard erosions.* (Proc. Soc. Exper. Biol. Med., v. 60, p. 387, Dec. 1945).

One-day old chicks were started on a special ration which has been found to result in erosions of the gizzard presumably because the ration lacked an anti-gizzard erosion factor. At four weeks of age these birds weighed 226 grams. They were killed and examined for gizzard erosions. The incidence of erosions was found to be 75 per cent.

Another group of day-old chicks were fed the identical ration to which was added 5 per cent of dried extract of the hog's upper intestine. This extract had previously been found to be effective in preventing the jejunal ulcer in Mann-Williamson dogs. At four weeks the average weight was 238 grams and the incidence of gizzard erosion was 67 per cent.

The negative results indicate that intestinal extracts do not contain the chick anti-gizzard erosion factor. — M. H. F. Friedman.

BRUNSCHWIG, A., JOHNSON, C. AND NICHOLS, S.: *Carbon tetrachloride injury of the liver: the protective action of certain compounds.* (Proc. Soc. Exper. Biol. Med., v. 60, p. 388, Dec. 1945).

Rats receiving 0.1 cc. of carbon tetrachloride subcutaneously showed in 24 hours characteristic hepatic lesions as determined histologically. The protective action of various agents was studied by administering these intraperitoneally immediately after the subcutaneous injection of the carbon tetrachloride. Similar histologic studies were carried out on the livers as in the control series of rats. An agent was considered to exert a protective action if at least 40 per cent of the animals tested showed either no lesions or lesions of limited extent.

Sodium thioglycollate and sodium glycollate gave 100 and 84 per cent protection respectively. Sodium thiosulfate and cysteine gave 30 and 38 per cent protection while glutathione gave 60 per cent protection. These substances were all administered in doses calculated to contain the same amount (6.2 milligrams) of sulfur.

The protective action against liver damage by carbon tetrachloride does not depend upon the presence of -SH in the agents. Such dependence upon the presence of -SH was found in the case of agents protecting against liver damage by chloroform. Apparently the intracellular disturbances produced by the two toxic substances represent different phenomena. — M. H. F. Friedman.

METABOLISM AND NUTRITION

BOUTWELL, G. K., GEYER, R. P., ELVEHJEM, C. A. AND HART, E. B.: *Interrelation of fats, carbohydrates and B vitamins in rat nutrition.* (Arch. Biochem., v. 7, p. 143, 1945).

The vitamin B complex requirements of the rat depend largely on the nature of the dietary fat and the dietary carbohydrate. The vitamin B deficiencies of rats fed on corn oil plus different carbohydrates varied in type with the nature of the carbohydrate. Glucose and galactose-glucose mixtures appeared to minimize the importance of the nature of the fat in determining the degree and extent of the vitamin B deficiency.

Lactose was inferior. Butterfat was much better than corn oil in resulting in a minimal vitamin B deficiency when fat-soluble vitamins were included in the mixed carbohydrate ration. The latter study was made on weanling rats. — G. Klenner.

MAUN, MARK E., CAHILL, WILLIAM M. AND DAVIS, RUTH M.: *Morphologic studies of rats deprived of essential amino acids. I. Phenylalanine.* (*Arch. Path.*, v. 39, p. 924, 1945).

Young rats fed phenylalanine-deficient synthetic diets composed of crystalline amino acids, crystalline vitamins, fats, dextrin, and the necessary salts were compared with paired fed rats given the same quantity of diet supplemented with phenylalanine. During the 28-day experimental period the animals of the deficient group lost weight, became weaker and appeared unkempt. They showed a reduction in hemoglobin and plasma proteins, narrowed epiphyseal cartilages of the long bones, a marked atrophy of the thymus, atrophy and decreased lipid content of the adrenal cortex, and a degeneration and atrophy of the testicular tubules. — Courtesy Biological Abstracts.

SELFRIDGE, GRANT: *Arterial spasm and fat metabolism: their relation to certain diseases and to certain members of the vitamin B complex.* (*California West. Med.*, v. 62, p. 163, 1945).

The bloods of a series of 37 tuberculosis patients (in the California Sanitarium at Belmont) all showed an increased ratio of fat to cholesterol. The importance of cholesterol in coronary disease has recently been emphasized, also its association with Meniere's disease. The factors of the B complex promise considerable relief from the spasm of blood vessels. — Courtesy Biological Abstracts.

CLARKE, DAPHNE, DE JONGH, T. W. AND JOKL, E.: *Effect of mid-day meal upon physical efficiency of school children.* (*Manpower (Transvaal)*, v. 1, p. 30, 1943).

With the help of the grid system of measuring physical efficiency (see de Jongh, Cluver and Jokl, *The Principle of Physical Performance Grids*), the three South African standard tests were applied on 2 occasions to a group of about 150 Indian female school children in Johannesburg, the first time during the Ramadan festival, i. e., a period when Mohammedan Indians adhere for a month to a dietary pattern referred to as "fast". During this period the ordinary daily feeding routine of 3 meals is reduced to 2, of which the first is taken very early in the morning. A large supper is served at 6:15 p. m. Throughout the day no food or drink is taken. The second series of tests was conducted with the same children 3 weeks after the conclusion of the "fast". The results of the 2 tests were statistically evaluated. Student's t-test for small sample groups was applied, a 5% value of P

being regarded as level significance. The "fast" had a significant negative effect on the 100 yards running performances. In respect to the 600 yards running test, the "fast" affected the younger children most. In respect to the shotput results, a significant retarding influence of the "fast" was noticeable in the case of the older females only. Analysis of body weights showed that the "fast" had caused significant loss. — Courtesy Biological Abstracts.

DYE, M., BATEMAN, I. AND PORTER, T.: *The effect of the level of protein in the diet on the utilization of vitamin A.* (*J. Nutrit.*, v. 29, p. 341, May, 1945).

Rats were kept on 9, 18, and 36% protein diets. Utilization of vitamin A was judged by weight gains, body length, and incidence of foci of keratinized epithelium. Up to an intake of 3 international units vitamin A per day the rate of gain was independent of the level of protein intake. On the 18% protein diet the weight gain was greatest and independent of the level of vitamin A. Polymorphonuclear cells increased on low vitamin A intakes. The normal midlingual-midlabial dentin ratio of the teeth was not in evidence until 6 units of vitamin A was included in the diet. — H. Stilyung.

BRIGGS, A. P., SINGAL, S. A. AND SYDERSTRICKER, V. P.: *A study of nicotinic acid restriction in man.* (*J. Nutrit.*, v. 29, p. 331, May, 1945).

The subjects of the study were two former pellagra patients. The diet of each was reduced in trigonelline so that only 3 milligrams of nicotinic acid were provided daily. One subject remained on the diet for 9 weeks, the other for 42 weeks. In both subjects the output of trigonelline dropped to a low level for the duration of the experiments. One patient had a low nicotinic acid excretion, in the other the excretion was normal. In neither patient were the initial minimal pellagra lesions increased. Failure in development of pellagra may have been due to synthesis of nicotinic acid by the intestinal flora and perhaps also to the absence of corn from the diet. The conclusion drawn from these studies was that under the conditions in which they were carried out a daily intake of 3 mg. niacin was in the vicinity of the minimal requirements. — H. Stilyung.

GROOTHUIS, M. J.: *Factors influencing phospholipid metabolism.* (129p. Thesis: Univ. Mich., 1943).

Quantitative changes in the liver lipids and liver phospholipids in the maturing rat (100-190 gm.) following the administration of cystine choline chloride, dl-methionine and elaidin were studied. Qualitative changes in the phosphoric acid portion were studied through the use of radioactive phosphorus. Changes in the liver lipid content of the adult rat resulting from the feeding of supplementary casein, and methionine

were also studied. Maintenance on the stock high-fat diets for 15-28 days produces an increased liver lipid content and a decreased phospholipid in the maturing rat. In the adult rat, the lipotropic action of a 20% casein diet is due to the methionine content. If the liver lipid content is high (15%) and the liver phospholipid content is lower than normal (3.2% of the moist fat-free liver) the oral administration of choline chloride or of methionine effects a decrease in the liver lipids within 8 hours after administration in 75% of the animals receiving the supplement. If the liver phospholipid content is low, administration of choline chloride, methionine, and elaidin effects an increase in the absolute amount of the choline chloride, cystine, and methionine always causes an increase in the "turnover" of the phospholipid P within 8 hours; elaidin leads to an increase in the "turnover" of the phospholipid P only when its administration also increases the liver phospholipid content. The phospholipid fatty acids could not be "labeled" by including elaidin in the diet; no evidence of the presence of elaidin acid in the liver phospholipid fatty acids was obtained. — Courtesy Biological Abstracts.

MISCELLANEOUS

BRUN, G. C.: *Pain and rectal tenesmus after injection of adrenaline into the colon.* (*Acta Med. Scand.*, v. 117, p. 448, 1944).

One to 1.5 ml. of 1/3 to 1% aqueous adrenaline solution was injected into the oral crus or the anal part of the colon of 23 patients on whom a colostomy had been performed. In 12 cases the injections induced sensations of flatulence, tenesmus, and severe colic-like pains. It is believed that pain at the site of the application was caused by a dilatation of arteries under the anemic area of the mucosa; also, that pain and tenesmi far from the site of application were due to reflex action with spasms or distentions and a resulting capillary occlusion leading to arterial dilatation in the underlying tissue as a pain-eliciting cause. — Courtesy Biological Abstracts.

ANDERSON, A. B.: *Lead content of urinary and biliary calculi and gall bladder bile.* (*Biochem. J.*, v. 39, p. 58, Jan. 1945).

Gall stones were found to have a lead content ranging from 0.3 to 65 milligrams per cent. The higher values for lead content were shown by the pure pigment stones. Gall bladder bile (obtained at autopsy) had a lead concentration ranging from 8 to 97 milligrams per cent (average: 38 milligrams). — N. M. Small.

HARTE, R. A.: *On the in vitro proteolysis of egg white.* (*Science*, v. 102, p. 563, Nov. 30, 1945).

Egg white has been reported to have a high biologic value for humans and dogs. Since dried egg white is used widely it was considered worth while determining the digestibility of dried and fresh egg white. Both peptic and tryptic digestion were studied. Coagulated egg white was found to be more digestible by both pepsin and trypsin than raw or dried egg white. No difference between the dried and undried raw albumens could be found. — I. H. Dougherty.

WINNICK, T. AND GREENBERG, D. M.: *Nomenclature of proteolytic enzymes.* (*Science*, v. 102, p. 648, Dec. 21, 1945).

The present tendency is to name different groups of proteinases after representative members. Thus enzymes with optimum activity in acidic solutions or with properties similar to pepsin are called "pepsinases". The authors suggest that the names for proteinases should be descriptive of their properties. The term "acidoproteinase" should be substituted for the "pepsinase" commonly in use. Similarly "neutroproteinase" and "basoproteinase" are descriptive of the pH region of the optimum activity of other enzymes. — I. H. Dougherty.

ALLISON, J. R.: *Hydrochloric acid and vitamin B complex deficiency in certain skin diseases.* (*Southern Med. J.*, v. 38, p. 435, April, 1945).

In all skin conditions which the author has studied in detail, there is a close association between absence of gastric hydrochloric acid and dermatologic conditions due to absence of the vitamin B complex. Consequently he advocates that proper benefits from vitamin B complex therapy can be obtained only if the hydrochloric acid deficiency is also considered and treated. — F. X. Chockley.

NOTICE

Dr. Anthony Bassler of New York City has been selected as Vice-President of the International Gastroenterologic Society and President of the permanent International Committee of the organization. The next convention will probably be held in England at some time when conditions of travel and accommodations are suitable.

Proceedings of the New York Diabetes Association, January 1945

OPEN MEETING

Under Auspices of the Committee on Internal Medicine
Saturday, January 13th, 1945, 8:30 p. m.
at

THE NEW YORK ACADEMY OF MEDICINE PROGRAM

Edward Tolstoi, M.D., Chairman, Committee on Internal Medicine, presiding

I. "WHAT IS THE CAUSE OF DIABETES MELLITUS IN MAN?"

Major L. Arthur Mirsky, M.C., U. S. A.

II. "THE USE OF CARBOHYDRATE IN DIABETIC ACIDOSIS"

John P. Peters, M.D., Professor of Medicine, Yale University, School of Medicine

III. DIABETES—ROUND TABLE DISCUSSION

A Panel was selected from the following members of the Council of the American Diabetes Association:

Joseph H. Barach, M.D., Pittsburgh; Russell M. Wilder, M.D., Rochester; Edward S. Dillon, M.D., Philadelphia; Cecil Striker, M.D., Cincinnati; Elliott P. Joslin, M.D., Boston; W. D. Sansam, M. D., Santa Barbara; L. H. Newburgh, M.D., Ann Arbor; R. T. Woodruff, M.D., Chicago; Herman O. Mosenthal, M.D., New York; Byron D. Bowen, M.D., Buffalo; Lester J. Palmer, M.D., Seattle; E. Roland Snader, M.D., Philadelphia; Seale Harris, M.D., Birmingham; Henry John, M.D., Cleveland; James E. Paullin, M.D., Atlanta; Samuel S. Alshuler, M.D., Detroit; L. Arthur Mirsky, M.D., Cincinnati; Howard F. Root, M.D., Boston; J. West Mitchell, M.D., Pittsburgh; C. H. Best, M.D., Toronto; George E. Anderson, M.D., Brooklyn; Frederick W. Williams, M.D., New York; Arthur R. Colwell, M.D., Evanston; Elmer L. Sevringhaus, M.D., Madison, and Joseph T. Boardwood, Jr., M.D., Philadelphia.

Dr. Edward Tolstoi—A year ago, the Committee on Internal Medicine of the New York Diabetes Association, under the guidance of Dr. George Anderson, sponsored a meeting to which the members of the Council of the National Association were invited. That was a memorable evening.

When I assumed the chairmanship of the Committee I appreciated that my task would be difficult since I was most anxious to approach, in some degree at least, the standards established by my predecessor.

While formulating my plans I was happy to learn of the Council's availability again this year, and because of this most fortunate circumstance it is my privilege to present to you as participants a concentrated array of talent consisting of brilliant investigators, keen clinicians and stimulating as well as inspiring teachers.

The order of the speakers will be changed as Dr. Peters wishes to make a train. He will, therefore, open our meeting. I am happy to present to you Dr. John P. Peters, Sterling Professor of Medicine, Yale University Medical School. He will discuss the Use of Carbohydrate in Diabetic Acidosis.

THE USE OF CARBOHYDRATE IN DIABETIC ACIDOSIS

DR. JOHN P. PETERS: This is really only a ruse on my part to escape the anticlimax of having to speak after Major Mirsky. I should really prefer to forego my speech and merely listen to Major Mirsky. The subject I am to talk about has been fought over for years since the discovery of insulin. My attitude towards it has been consistent. I have advocated the administration of glucose in the treatment of diabetic acidosis. This is, I believe, based on sound physiological premises which I shall briefly review. Although the effect of starvation on metabolism was discovered so early, it has taken a long time for its implications to be recognized in medicine. That starvation reduced carbohydrate tolerance was first reported by Lehmann in 1874 and again noted by Hofmeister in 1890; the nature of the disorder was quite thoroughly analyzed by Bang early in this century. Since then it has been exhaustively studied. When an animal, accustomed to subsist upon a diet containing preformed carbohydrate, is starved completely or deprived of all exogenous carbohydrate, its tolerance for carbohydrate decreases. This has been demonstrated in man, in rabbits, and in limited experiments in monkeys. This intolerance reaches maximal intensity when hepatic glycogen is exhausted. It appears, however, to be connected not with the state of the hepatic glycogen stores per se, but to occur when the animal is subsisting on a metabolic mixture composed entirely or almost entirely of protein and fat. Under these circumstances the production of ketone bodies from fat by the liver is greatly accelerated. It has been suggested that these 4-carbon groups are substituted for 4-carbon groups usually derived from carbohydrate. If, in this condition of starvation an animal is given a dose of carbohydrate, it develops an excessive hyperglycemia which may be great enough to provoke glycosuria. Although most of the glucose is retained, for a considerable period the non-protein respiratory quotient does not rise, but remains at or near 0.7, indicating that only fat and protein are being oxidized. Only after a considerable amount of carbohydrate has been given does it rise above this level. If a man who has subsisted on a mixture of protein and fat, whether endogenous or exogenous, is given carbohydrate, there is an interval in which carbohydrate is not burned, but only used to form liver glycogen. Combustion of carbohydrate is not re-established until this process has advanced to a certain point. There is evidence that during this interval the effectiveness of insulin is also diminished. It is not altogether relevant, but may be worth mentioning here, that insulin itself may produce starvation diabetes by deglycogenating the liver when exogenous carbohydrate is not available. I would venture to say that

some of the greatest difficulties in the regulation of diet and insulin in diabetes arise from the occurrence of starvation phenomena at intervals, which is inevitable when food and insulin are given at intervals and activities vary.

Other things being equal, the combustion of carbohydrate is accelerated by hyperglycemia. This is to be expected since the oxidation of carbohydrate is effected by chemical reactions in which glucose is one of the reagents. In the normal person these reactions are so much accelerated by hyperglycemia that it is almost impossible to produce glycosuria by the oral administration of sugar. Klatskin has shown that there is a direct relation in diabetes between the initial height of the blood sugar and the reduction in milligrams per cent produced by a given dose of insulin. For a long time it was held by moralists that infractions of diet precipitated ketosis. All physiological and chemical evidence, on the other hand, indicates that carbohydrate should diminish ketosis. Mirsky has demonstrated that patients do not develop ketosis merely because they do not behave themselves according to the dictates of their physicians, as far as diet is concerned. If they take extra carbohydrate they need less insulin to eliminate ketosis. The sugar brings evils of its own. I presume that some of Mirsky's patients were put to no little inconvenience when they had to excrete as much as 12 liters of urine in 24 hours. But it is clear from his experiments that despite this the ketosis diminished.

Diabetic acidosis and the coma in which it culminates mark the most extreme diabetic state. Carbohydrate combustion is reduced to an absolute minimum. In no other known condition is there such complete starvation. I see no reason to believe that the diabetic is protected by divine providence from the consequences of starvation. The existence of diabetes does not remove him from the realm of physiological reactions. One reason, I think, that the use of glucose in diabetic acidosis has been decried is the feeling that, since there is hyperglycemia, there is a large store of available glucose in the body. Unfortunately, the concentration of glucose in the blood has always been expressed in terms of milligrams per 100 c.c., while in the diet it is expressed in grams. This gives an exaggerated impression of the quantity of glucose in the body, which is the only reserve of carbohydrate that the patient possesses. The liver, in this state, is probably quite deglycogenated. The glucose in the body, under these circumstances, is derived entirely from protein and the glycerol of fat, and large proportions of it are constantly lost in the urine. Before such a patient can burn carbohydrate it is necessary to build up a certain amount of liver glycogen. In a series of cases with diabetic acidosis we tried to evaluate the utilization of glucose by analyzing urine and both capillary and venous blood for sugar at frequent intervals. We were convinced that in the first two to four hours, despite the most vigorous treatment, no more glucose was used than could be accounted for by the amounts required to form glycogen in the liver.

We have given glucose to accelerate this process, re-

gardless of the blood sugar. I do not mean to imply that there is no limit to the quantity of sugar that can be utilized nor to the degree of hyperglycemia that facilitates the combustion of sugar. It was demonstrated by Wierzychowsky that there is such a limit in the normal animal, at about 2000 mg. per 100 c.c. of blood or higher. After this lag the blood sugar begins to fall and, when it does so, may drop rather quickly. In fact the drop may be so precipitate that the patient develops symptoms of hypoglycemia. To superimpose insulin shock upon the already existing circulatory collapse of diabetic acidosis is most unfortunate. The prevention of such a catastrophe is another reason for giving glucose. We begin with small doses of glucose and large doses of insulin in the first few hours. As soon as the blood sugar begins to fall definitely the amount of insulin is diminished while the dosage of glucose is increased. I believe that a large proportion of diabetics who have been pulled through acidosis succumb to shock in subsequent hypoglycemia which has escaped recognition. If the hypoglycemia is allowed to continue long enough, the liver again becomes deglycogenated and the patient may revert to a state of acidosis from the consequent starvation. It is our custom to give about 25 gm. of glucose intravenously in 10 per cent solution with about 50 units of insulin as soon as the patient is seen. After that glucose is given at the rate of about 10 gm. per hour until the blood sugar begins to descend, when the rate is increased. Large amounts of saline are also given. This is injected subcutaneously, not intravenously, for two reasons. In the first place this avoids the danger of embarrassing an impaired circulation or aggravating the condition by reducing the serum protein. Moreover, the subcutaneous fluid serves as an index of the state of the circulation. If the saline is not absorbed from the subcutaneous tissues it may be inferred that the circulation is not adequate and transfusion is indicated.

I have stated the arguments for the use of glucose in diabetic acidosis in purely physiological terms. I shall refrain from illustrating these arguments with case reports because this would be likely to reduce the discussion to the level of an experience meeting.

Dr. Tolstoi: Thank you, Dr. Peters, for a most interesting presentation. This paper is now open for discussion.

Dr. Root: Everyone familiar with the treatment of diabetes before the discovery of insulin knows that undernutrition and even starvation treatment relieved diabetes. Starvation reduces ketosis in diabetes because it lowers the total metabolism. The effect of starvation in diabetes is not at all the same as in the normal human being because of the difference in insulin reserve.

Diabetic coma is due to relative or absolute insulin deficiency. It begins with hyperglycemia and not hypoglycemia. Its course is due to the increasing lack of insulin in relation to total metabolic needs. Serious acidosis and coma are not relieved by the administration of glucose alone. The experiments of Mirsky, who gave diabetic patients receiving insulin in hospital wards excessive amounts of glucose without producing acidosis, are not to be compared with the breaking of a diet by a patient living outside the hospital on levels of activity quite

unlike those in the hospital. Indeed, Mirsky has been greatly misquoted by those who have used his observations to support the idea that large amounts of glucose are needed in coma. Actually, Mirsky warned specifically against the use of glucose in large amounts in patients with diabetic coma because of the danger of pancreatic exhaustion.

I know of no reason for the belief that increasing the blood sugar in diabetic coma increases carbohydrate utilization. Actually as the blood sugar rises and acidosis increases the utilization of carbohydrate steadily diminishes in coma.

Much is said about the use of glucose in order to build up glycogen reserve in the liver but no real evidence exists that carbohydrate oxidation is dependent upon the level of glycogen storage in the liver. Actually in the slide shown the livers of two patients dying in coma are shown to be stuffed with glycogen. In each case glucose was given during coma in amounts greatly in excess of immediate caloric needs. Did this overfeeding with glucose and excess deposition of glycogen in the liver exert a harmful influence? Let us examine the liver of a normal non-diabetic dog given excessive glucose intravenously in the laboratory of Astwood and Krayer of the Harvard Department of Pharmacology. This dog's liver is also filled with glycogen and the dog died of liver failure with jaundice, falling serum protein, prolonged prothrombin time and anuria. The dog received 1.8 grams glucose per kilogram body weight per hour and died in 70 hours. The dog thus received 7 calories in glucose per hour when he needed only 2 calories. Thus feeding glucose by vein at a rate in excess of caloric needs will kill even a normal animal. Is this the explanation of the harmful effect of excessive glucose administered beyond the hourly caloric needs of the patient in diabetic coma?

Actually in diabetic coma the object of treatment is to bring about oxidation of glucose so that carbohydrate oxidation will take the place of the excessive fat oxidation and ketone formation. Sufficient insulin must be given until the insulin resistance of acidosis has been overcome. Undoubtedly one of the effects of insulin is to protect the liver. It may well be that the explanation for the disappearance of ketonuria and ketone bodies in the blood as severe coma nears its fatal termination is due to liver failure and the consequent failure of the liver to permit ketone body formation.

Actually, Dr. Tolstoi, may I suggest that it would be a topic of great interest if at next year's meeting of the New York Diabetes Association an attempt were made to present pathologic evidence of glycogen storage in the liver not only in relation to coma but to other phases of diabetes.

Dr. Allan Butler: I want to add one little bit of information as a person who is familiar with one of Dr. Root's slides. It comes from a patient whose case I was asked to discuss at a pathological conference (New England Journal of Medicine, November 9, 1944). I was astonished when the pathologist told me that this liver had considerable glycogen because the patient had received only 100 grams of glucose in the 16 hours of therapy. Moreover, he received this glucose after six hours of intensive insulin and hydration therapy and at a time when the urine contained no glucose but still contained acetone. I wonder how many other people in the audience were also astonished to see a liver which contains that much glycogen when only 100 grams of glucose had been given. The pathologist couldn't say that there was any damage to the liver cells as the result of excessive glucose. To suggest that such parenteral glucose or that the glycogen in the liver was related to the death of the patient seems totally unjustified. Moreover, to suggest a similarity between this case and the experiments of Astwood, Flynn and Krayer on dogs is unwarranted.

Their dogs received glucose in excess of their caloric expenditures. This patient received but 100 gm. of glucose or but 400 calories in 16 hours.

Dr. Wilder: I have no special comment to make. I can't answer this question about glycogen as I don't know anything about it. I was interested in asking Dr. Peters whether he thought that there might not be some other explanation of this effect on the tolerance, and of giving insulin even to normal people on sugar tolerance. Some of us have flirted with the idea too if you put any endocrine organ to rest then it went to functional atrophy. In Toronto Best found that such a pancreas revealed a lowered content of insulin. How much bearing this has on the point Root raised I admit I don't know. I was rather interested in Peters' suggestion that the diabetic developed a starvation diabetes on top of his insulin deficiency diabetes. I am not quite willing to accept that at once without thinking about it more.

Dr. John: I think Root misquoted Peters and did not say what Peters actually said. If you get a patient in diabetic coma with a marked hyperglycemia, if you would load him up with glucose you would not be contributing anything to that patient's progress—that isn't what Peters said. Peters said, I think, that a patient needs small doses of glucose plus high doses of insulin, and not letting that patient go into hypoglycemia. Nothing more to state except that it is all wrong to give such a patient large doses of glucose. I can't see any sense in that—nobody can. Clinically Peters' observations have certainly been proven. A patient who is dehydrated needs liquids intravenously. The answer to it is that with such treatment of diabetic coma the mortality has been low.

Dr. Tolstoi: I should like to call on Dr. Peters for any rebuttal he might wish to make.

Dr. Peters: I again apologize that I should be taking more of Major Mirsky's time. If I gave the impression that I believe insulin is unnecessary in diabetes, let me remove that impression at once. The action of insulin is, however, conditioned by other metabolic factors. For example, it has been proved by experiment that a small amount of insulin with exercise will do what only a large amount of insulin can do without exercise. Starvation will make insulin less effective. Dr. Root stated that he never saw diabetic coma which originated from hypoglycemia. I could describe such cases if I had not promised to refrain from case reports. I think Dr. Root's remarks about the quotation from Dr. Mirsky should be answered by Dr. Mirsky. The reaction of the metabolic processes towards glucose derived from endogenous source differs from the reaction towards preformed glucose. Dr. Best spoke about the fact that I attributed too much importance to the amount of glycogen in the liver. I was careful to say that the phenomenon of starvation diabetes is not directly connected with liver glycogen, but with the fact that the animal is subsisting solely upon protein and fat. If an animal possesses the ability to burn carbohydrate the rate of combustion can be influenced by other factors than insulin. If larger amounts of glucose are given, the amount of sugar burned increases, provided the animal possesses some ability to burn sugar.

As to the reports of the patients whose livers were presented on the screen by Dr. Root, I am left cold. One cannot say that because he disapproved the treatment that a patient received, the patient necessarily died as a result of this treatment. I see no reason to believe that the experiments with the dog that he presented have any relevance to the use of glucose in the treatment of diabetic acidosis in man. I do not advocate drowning people with glucose solution. The object is to restore liver glycogen and to accelerate the combustion of car-

bohydrate. This may be done with relatively small amounts of glucose, of the order of 100 grams. Dr. Root mentioned that the diabetic animal cannot convert carbohydrate to fat. There is no reason to regard this as a distinct disability. The conversion of carbohydrate to fat requires the expenditure of a certain amount of energy which can be derived only from the combustion of part of the carbohydrate. Obviously the conversion cannot be effected if the ability to burn carbohydrate is abrogated; but can be resumed when this ability is restored by the administration of insulin.

Dr. Tolstoi: In view of the fact that there is a round table discussion coming up and some of the questions bear upon this topic, I think we will proceed with the program and possibly this subject will come up again later on. The next speaker has already been mentioned by Dr. Peters. He is Major I. Arthur Mirsky, who will speak on "What is the Cause of Diabetes Mellitus in Man?"

Dr. Mirsky: My neck is away out and much as it has been chopped at, I am sure that that is nothing to what will happen after I get through with my paper. I said that I would be willing to take up a provocative subject for discussion as I was told that a battle was what was wanted.

"WHAT IS THE CAUSE OF DIABETES MELLITUS IN MAN?"

by

I. ARTHUR MIRSKY, MAJOR, M. C.

THE FAMILIAR syndrome of diabetes mellitus in man is the resultant of a variety of metabolic disturbances concerning which much is known. However, the initial abnormality which is responsible for the metabolic deviations, i. e., the primary cause, is unknown. It cannot be emphasized too much that the hypotheses which have been developed thus far in explanation of the pathogenesis of the syndrome in man are purely inferential and based upon observations of experimental situations in animals. Species differ so much, that observations made in one species frequently do not apply to another species; the gap between man and any other animal is extremely large even when judged on the basis of crude structure, let alone when compared from the functional point of view.

Ever since 1788 when Cawley (1) reported his autopsy findings of pancreatic calculi in a patient dying of diabetes mellitus, the pancreas has been associated in an etiologic sense with diabetes. The demonstration in 1889 by von Mering and Minkowski that complete pancreatectomy in the dog resulted in the production of a syndrome analogous to the diabetes of man lent further credence to the role of the pancreas. This seemed established in a decisive manner in 1922 when the brilliant observations of Banting and Best were reported (2). The prompt availability of insulin for clinical trial in man and the excellent therapeutic responses which ensued seemed to leave little doubt that pancreatic insufficiency was responsible for the initiation of the diabetic syndrome in man.

The fact that insulin is equally efficacious in the treatment of both the diabetic human and the depancreatized dog does not mean that man need have an inadequate pancreas. All it does indicate is that both

the patient and the dog need more insulin than they are producing and consequently suggests that a relative or absolute insufficiency of insulin is the main hormonal defect in the patient with diabetes mellitus. This makes it all the more important to realize that it is essential to distinguish between an insufficient pancreas and an insufficiency of insulin.

An insufficiency of insulin can be brought about 1) by a decrease in the production of insulin or 2) by an increase in the utilization, destruction or inactivation of insulin or 3) by both. The theory that is generally accepted today is that in human diabetes, the insulin insufficiency is brought about by a deficiency in insulin production. This thesis has been excellently developed recently by Lukens (3).

The focal point of the pancreatic insufficiency hypothesis is that the diabetic human has inherited an inadequacy with respect to the functional capacity of the Islets of Langerhans, i. e., his insulin reserve is inadequate. Upon this inadequacy are superimposed inherited or acquired factors which create so great a demand for insulin that an added strain is imposed on the Islets and they then fail. Insulin production is then diminished and the insulin insufficiency which ensues precipitates the metabolic disturbances responsible for the syndrome of diabetes mellitus.

Clinical observation and genetic analyses in man amply support the concept that a tendency to diabetes may be inherited. However, evidence is still lacking to decisively indicate that the inherited tendency to diabetes is related to the inheritance of a functionally inadequate pancreas.

Differences in animal species have been presented as an index of varied inherited susceptibilities (3). Thus the dog is the only animal which responds to the injection of anterior pituitary extracts with the production of a permanent diabetes; other species do not do so unless a partial pancreatectomy has been performed before the injections are started. Consequently, it has been stated that the dog has inherited a relatively smaller insulin reserve than the cat or rat, for example, and for that reason it responds so easily to diabetogenic extracts which presumably increase the demand for insulin production.

Young's more recent observations (4) lead us to question this type of argument. He found that during the period of natural growth in the puppy, the administration of a pituitary extract which is diabetogenic in the adult animal leads not to diabetes but only to growth. When, however, the puppy has reached adulthood under continuous pituitary treatment, it became diabetic. Estimations of the amount of insulin which the pups must have been producing to counteract the diabetogenic action of the extracts reaches phenomenal levels. Surely if the diabetes that results in the adult dog when treated with pituitary extracts is due to a relatively functionally inadequate pancreas, the puppy's pancreas should be at least as capable of failure, if not more so.

There are species, like the duck, for example, which have pancreases capable of manufacturing insulin as

indicated by their insulin content, and yet when these glands are removed (5) or the islets destroyed with alloxan (6) diabetes does not follow. Nor does the administration of pituitary and other glandular extracts to such depancreatized ducks produce diabetes. Does this mean that the duck has inherited a poor pancreas or poor pituitary or does it mean that the duck has inherited an increased resistance to diabetes in the form of some mechanism whereby carbohydrates can be utilized with or without the mediation of insulin? The fact that glucose degradation and oxidation can take place without the mediation of insulin in cell-free extracts and in some systems consisting solely of suitable substrates, enzymes and their co-factors, without the benefit of insulin, supports the possibility that similar phenomena may occur "in vivo" in some species.

Too many unknown factors still exist and until they are identified and their functions clarified, blaming the predisposition to diabetes in man on the inheritance of a pancreas which has inadequate reserves may be merely a convenient oversimplification.

Experimental permanent diabetes in the dog has been the main source of data upon which the pancreatic insufficiency concept is based. This type of diabetes has been produced by four procedures: 1) by the removal of more than 4/5 to 9/10 of the pancreas; 2) by the removal of a sufficiently large proportion of the pancreas and subsequently permitting the ingestion of an excess diet; 3) by the injection of crude saline extracts of the anterior pituitary into suitable animals; and 4) by the injection of alloxan.

Removal of the whole pancreas results in the development of diabetes in most species. If more than 15% of the pancreas is left intact, diabetes may not occur. However, if less than that amount is left, diabetes will usually occur because the remnant will undergo degeneration. One cannot overemphasize that from 80-95% of the pancreas must be removed or destroyed before diabetes will ensue in the dog or cat.

Alloxan diabetes is analogous to that produced by total pancreatectomy since alloxan acts by producing a rapid, progressive degeneration and necrosis of the beta cells of the Islets. Alloxan is an Islet toxin and as yet has not been demonstrated to be a factor in the production of human diabetes (7).

A third form of experimental diabetes is that which occurs when the partially depancreatized dog is given a liberal diet. Homans (8), and especially F. M. Allen (9), showed that removal of a large part of the pancreas in dogs led to diabetes if the dogs were not put on a relatively restricted diet. Usually, hydropic degeneration of the beta cells of the Islets of Langerhans developed and subsequently atrophied. Allen attributed these changes in the Islets to exhaustion as a result of overwork since he could demonstrate that the administration of a restricted diet prevented the development of hydropic degeneration and the associated diabetes. After insulin became available, Copp and Barclay (10) and Bowie (11) confirmed the overwork hypothesis when they found that treatment with insulin prevented or alleviated the degenerative changes in the

pancreatic fragment in such partially depancreatized dogs.

More recently Haist and Best (12) found that when a portion of the pancreas was removed from dogs and the animals did not become diabetic, the concentration of insulin in the remnant remained within normal limits. Where sufficient pancreas was removed so that the animals did become diabetic, the insulin concentration in the remnant fell markedly. Which came first, the hyperglycemia or the fall in insulin content of the pancreas? Lukens believes that it is the hyperglycemia and not the insulin content of the pancreas which is the factor responsible for the development of Islet lesions. In other words, Islet lesions and insulin impoverishment occur in partially depancreatized only after hyperglycemia has developed. However, Best and his co-workers present the possibility that the amount of circulating insulin may be the decisive factor in determining Islet activity.

That the amount of circulating insulin may be the decisive factor controlling the production and secretion of insulin by the pancreas is suggested by a number of phenomena. Thus the administration of exogenous insulin results in a decrease in the production of insulin by the pancreas (12) just as the administration of corticosteroids will diminish adrenal cortical activities. Further, permanent diabetes mellitus can be produced in the partially depancreatized dog by the persistent administration of insulin which so inhibits the endogenous production of insulin by the pancreatic remnant that a "disuse atrophy" results (13). Hyperglycemia plays no role in this phenomenon. Accordingly, it can be postulated that if the circulating insulin be diminished for one reason or another, the pancreas would have to increase its secretion in order to maintain the insulin concentration of the blood and upon failing to do so, hyperglycemia would result. Hence it is quite possible that hyperglycemia is the result rather than the cause of Islet degeneration. Moreover, it must be noted that Allen found that keeping the blood sugar at normal levels or below by the administration of phlorrhizin did not prevent the development of the degenerative changes in the pancreas. This is not in accord with the more recent studies of Lukens and his co-workers.

The diabetes that is produced by the injection of extracts of the anterior pituitary has been studied extensively in recent years. That the injection of an extract of the anterior pituitary gland will produce hyperglycemia and glycosuria has been known since 1927 but the significance of these findings were not generally appreciated until Young demonstrated conclusively in 1937 (14) that if the course of injection of anterior pituitary extracts was sufficiently severe and prolonged, diabetes persisted indefinitely after the injections were discontinued. Shortly thereafter it was established that the pancreases of these permanently diabetic animals contained fewer than normal Islets. Granule staining showed that the lack of granular beta cells was almost complete.

Best and his colleagues (12) in a series of papers

reported on their findings that the insulin content of the pancreas of such permanently diabetic dog was extremely low, that during the course of the injection of anterior pituitary extracts, and before the diabetic state had become permanent, there was a progressive reduction in the insulin content of the pancreas. This reduction in insulin content paralleled the progressive degranulation of the beta cells of the Islets of Langerhans. The degranulation was followed by hydropic degeneration of the beta cells.

Accordingly, the Islet changes in the pituitary-injected dog closely resemble those found in partially depancreatized animals. Also, the reduction in the insulin concentration in the pancreatic remnant of the partially depancreatized animals is similar to the change in the insulin level found in the pancreas of animals receiving injections of anterior pituitary extracts. In both instances, overwork and subsequent exhaustion is believed to be the cause of the changes.

Best, Campbell and Haist report an interesting invert relationship between the fasting blood sugar level and the concentration of insulin in the pancreas of the pituitary injected dog. When the injections of the extract were discontinued the blood sugar fell rather quickly to the normal value, but the insulin content of the pancreas remained low until *after* the normal blood sugar level was restored. These findings seem to suggest that the blood sugar level is the cause of the Islet changes rather than the reverse. However, Haist (12) emphasizes the fact that the experiments are not conclusive in this regard and that the authors *do not assume* that the hyperglycemia is the main factor, since diabetogenic pituitary extracts have profound extra-pancreatic effects (15), and that the concentration of insulin in the circulation may still be the decisive factor.

The studies of Lukens, Dohan and Wolcott (16) lend support to the view that the pancreatic damage which follows pituitary treatment is associated with the hyperglycemia induced by the extracts. They demonstrated that the hydropic degeneration consequent to the administration of pituitary extract could be prevented if hyperglycemia is first prevented by the administration of insulin or phlorrhizin. Lukens believes that the weight of evidence appears to support the concept that the level of blood glucose is a factor of prime importance in the pathogenesis of both forms of experimental diabetes and that hydropic degeneration occurs only after hyperglycemia has been produced. However it is important to note that Houssay (17) could not produce the pancreatic changes by keeping the blood sugar elevated by means of a constant injection of glucose. Further, the administration of phlorrhizin to dogs (18) and man (19) has been shown to aggravate rather than ameliorate diabetes.

It is also important to note again that the injection of pituitary extracts will produce diabetes through pancreatic damage *only in dogs*. Other species do not respond in a similar manner unless they have been partially depancreatized. Further, in many species, e.g., the rat, the *same pituitary extract which is dia-*

betogenic in the dog stimulates the pancreas to the production of greater amounts of insulin. Little evidence exists as to where man fits in, since injections of anterior pituitary extracts have generally been ineffective.

It is evident from the preceding that pituitary diabetes is in many respects identical with experimental pancreatic diabetes. However, important differences do exist (e.g., an increased insulin resistance in the former) and are usually disregarded by those who advocate the hypothesis that hyperglycemia is of prime importance in the development of experimental diabetes and the associated pancreatic lesions. These differences will be considered later.

How do the studies on experimental diabetes apply to human diabetes? Obviously if the concept that human diabetes is solely the result of pancreatic insufficiency, be it due to direct or indirect causes, one must expect to find extensive pancreatic damage. Further, if the pancreatic insufficiency results from hyperglycemia consequent to overeating or the presence of endocrinopathies, the pancreatic lesions should be primarily *hydropic degeneration* in character since that is the characteristic lesion which occurs in experimental diabetes.

The question of the relation of Islet lesions to diabetes has been the subject of numerous studies for a long time. In Warren's own series of 271 diabetics, he found that 25.5% showed no morphologic abnormality (20). Another 25.5% showed a fibrosis of the beta cells of which only 2.9% showed marked changes. Hyalinization was present in 37.8% of the cases, being well worked in 15.5%. Hydropic degeneration was present in only 5.5% of the cases. It is noteworthy that only 24% of the cases showed considerable damage and that the characteristic lesion of the experimentally induced pancreatic insufficiency was relatively rare. The most prevalent lesion was hyalinization of the Islets.

It might be stated that hydropic degeneration is an evanescent lesion and thereby explain its rarity in man. That might be the case if therapy resulted in cure, but cannot be proposed when the patient dies with active diabetes and when sufficient atrophy to account for the lesion is not found.

The postmortem diagnosis of diabetes mellitus has in the past been dependent primarily upon the demonstration of hyalinization of the Islets of Langerhans, and until 1904 that was considered a specific change of diabetes mellitus. Since then, however, it has been demonstrated by numerous observers that hyaline degeneration occurs in non-diabetics, and is not pathognomonic of diabetes.

Gellerstedt (21) found that of 110 consecutive post-mortem examinations of patients aged 50 to 90 years, 46.3% had hyaline degeneration of the Islets. Only three of these were diabetic. In a study of 200 pancreases from individuals of from 72 hours to 87 years of age, Arey (22) noted hyaline degeneration in the pancreas of 16.6% of 114 non-diabetics older than 50 years and no degeneration in 34 cases under that age.

71.7% of 46 diabetics over 50 years of age revealed lesions while 50% of 6 diabetics under that age showed similar lesions.

Arey emphasizes that one must consider the possibility that hyaline deposits are entirely independent of the diabetes, since they are more frequent in the older aged groups. One factor that diabetics and old people have in common is vascular disease, which in turn, is known to be far more severe in diabetics than in non-diabetic patients of the same age. As yet there is very little evidence that the vascular diseases found in diabetics are due to lack of insulin. Modern therapy has not reduced the incidence of vascular disease sufficiently to suggest that possibility. It is just as probable that these vascular diseases are associated diseases rather than complications of diabetes. Therefore, it is possible that hyalinization of the Islets is not dependent upon the diabetes, but is merely a senile change depending upon vascular disease, and, therefore, accentuated by one of the concomitants of diabetes. The fact that hyalin deposits are less frequent in young diabetics than in old diabetics favors this view.

In a recent study on intercapillary glomerulosclerosis in diabetes, Laipply, Eitzes and Dutra (23) noted that 63.7% of their diabetic patients had this renal lesion, while hyalinization of the Islets of Langerhans was found in 63.1%. Thus, intercapillary glomerulosclerosis was just as common as hyalinization of the pancreatic Islets of patients who had diabetes mellitus. On the other hand, glomerular lesions occurred only in 2.4% of non-diabetics while slight hyalinization of the pancreatic Islets was present in 13%. From their data the authors indicated that *intercapillary glomerulosclerosis is a more specific anatomic lesion in diabetes than is hyalinization of the Islets of Langerhans!* Should it be regarded of etiologic significance in the pathogenesis of human diabetes especially in view of Reinecke's (24) observations that the kidney can make glucose?

Scott and Fisher (25) found that the insulin content of the pancreas in 14 non-diabetic human subjects average 1.7 units per gram of pancreas. In 18 diabetics the insulin concentration averaged slightly less than 0.4 units per gram of pancreas, i.e., about 25% of normal. However, careful analysis of their data reveals that while the normal subjects consisted chiefly of individuals who were killed by accidents, the diabetic group consisted of patients who died in consequence of a variety of complications, such as anuria, pneumonia, coma and chronic myocarditis. Obviously comparison between the groups is not justified in view of the relatively debilitated state of the diabetics which in itself would reduce the insulin content and cause a reduction in the granulation of the beta cells of the Islets as may be inferred from Best's studies. In spite of this criticism, it is interesting to note that one severe diabetic's pancreas had an insulin content of 1.9 units per gram!

In a recent discussion Joslin stated that "to prove that trauma causes diabetes one must show that the pancreas is gravely injured. In fact, at least 4/5 destroyed, probably 9/10" (20). Surely this must be

true also for spontaneous diabetes in man. Yet most authors attribute human diabetes solely to pancreatic insufficiency although it is obvious from morphologic studies and even insulin assays of pancreases from diabetics that destruction of over 80% of the pancreas is a rarity in the human. Some go to such extremes as to imply that glucose will so rapidly exhaust the pancreas that complete insufficiency and even death can be induced in diabetic coma by the injection of as little as 100 grams of glucose (27).

The fact that about 25 per cent of diabetics show no morphologic damage in the pancreas and that a severe diabetic may have a high insulin concentration in the pancreas is too readily forgotten. If diabetes in man is due to pancreatic insufficiency alone, why are there any diabetics with a normal pancreas? Further, one might ask as to why the pancreas from acromegalic diabetics may show evidences of an increased insulin production as indicated by hyperplastic Islets instead of the hydropic degeneration noted in the Islets of anterior pituitary treated dogs (28).

The crucial blow to the pancreatic insufficiency theory comes from the recent publications on the diabetes that ensues in consequence of complete pancreatectomy in man. Rockey (29) studied a man whose carcinomatous pancreas he had removed and who survived 15 days. During this period the patient received 150 gm. of glucose daily and his glycosuria could be controlled with 27 units of insulin. At autopsy, a very small amount of pancreatic tissue was found, but not enough to have kept him from being analogous to the completely depancreatized dog. Brunswick (30) described a similar case in which almost as little tissue remained. His patient has survived two and one-half years without clinical evidence of diabetes. Priestley's patient who recovered from total pancreatectomy developed diabetes which was controlled by 30 units of insulin daily (31). More recently Goldner and Clark (32) reported two cases who underwent total pancreatectomy, one of which died on the 11th day from gastric hemorrhage and the other on the 10th day from hepatorenal failure and uremia. One patient was maintained with about 50 units of insulin and a daily glucose intake of 150 to 200 grams, and the other required 40 units of insulin daily with a glucose intake of from 150 to 200 grams. These experiences with depancreatized man reveal that they require less insulin and are more sensitive to insulin than are many human diabetics.

From the preceding analysis it may be noted that although experimental diabetes mellitus occurs only when over 4/5 of the pancreas is destroyed, the pancreas from human diabetics usually shows either no abnormality whatsoever or much less than 80 per cent destruction; that although the histologic lesion associated with experimental diabetes is a hydropic degeneration, only about 5 per cent of human diabetic pancreases have this lesion; that although dogs develop hydropic degeneration of the pancreas after extensive anterior pituitary injections, human diabetic subjects with hyperpituitarism generally do not reveal such

lesions; that although pancreatectomy produces diabetes in man, much less insulin is required for the maintenance of such patients than could be anticipated from the amounts necessary in clinical diabetes.

To these considerations can be added a number of questions which have hitherto received no adequate explanation. Why should a human diabetic ever need more insulin than his pancreas is apparently capable of producing? Why does the human diabetic ever become so resistant to the action of insulin that fantastic quantities must be administered in order to elicit a physiologic effect? Why is obesity so frequent in the early history of the diabetic? Why should an infection apparently increase the demand for insulin in the diabetic who is already receiving large quantities of exogenous insulin? These and other questions cannot be answered fully on the basis of the pancreatic insufficiency concept. Thus, for example, the obese patient who later becomes a diabetic may show no hyperglycemia until his disease appears and consequently hyperglycemia cannot be blamed for the subsequent syndrome. Further, the depancreatized dog will require an increased amount of insulin in the presence of infection, a phenomenon which cannot be attributed to a decrease in insulin production (33). All these considerations do not support the hypothesis that human diabetes is due solely to the inheritance of a pancreas which has an inadequate reserve capacity and therefore breaks down under stress. The only conclusion that can be made from the facts discussed is that insulin insufficiency, not pancreatic insufficiency, is the cause of diabetes mellitus in man.

In order to explain the various phenomena referable to the etiology of diabetes in man, one must *speculate* about possibilities which are still unknown, a procedure which is subject to justifiable criticism. Thus, one can postulate that an insufficiency of insulin may ensue whenever the rate at which it is used up by the tissue exceeds the rate at which it is secreted by the pancreas. This may be accomplished by 1) an increased demand consequent to those unknown chemical phenomena for which insulin is essential "in vivo," 2) an excessive rate of insulin destruction, and 3) an inactivation of insulin consequent to the development of specific antibodies or other insulin antagonists. Since these are very few facts relative to this hypothesis, we shall restrict our discussion to some pertinent examples.

The precise role played by insulin is a total mystery. It is suspected that insulin plays some part in the interrelationship between carbohydrate and phosphorus metabolism in that it may have something to do indirectly with pyruvate oxidation. Whatever its precise chemical participation may be, it is obvious that insulin is destroyed concomitant with or subsequent to its action. Hence, it can be postulated that with an increase in the turnover of various substrates and particularly carbohydrate, an increase in the rate at which insulin is used up will ensue, and therefore, an increase in the necessity for more insulin will follow. In other words, an increase in the utilization of carbohydrates either

for storage, oxidation or conversion to fat will result in an increased demand for insulin.

When appetite is so affected that an excessive intake of food results, it is probable that an increased utilization of insulin takes place as is indicated by the diabetes which occurs in the partially depancreatized dog and the increased concentration of insulin in the pancreas of the carbohydrate fed rat. The normal human pancreas can compensate adequately for this increased demand by producing more insulin. It is even quite probable that periods of overcompensation may occur with a resultant temporary hypoglycemia and consequently further increase in appetite, thereby initiating a vicious cycle. However, when the compensatory increase in insulin production and secretion by the pancreas has reached a maximum and begins to lag behind the rate of insulin utilization, a relative insulin insufficiency will ensue. Decreasing the food intake will decrease the insulin demands and consequently result in a disappearance of the relative insufficiency. The elderly obese patients with hyperglycemia who become normal when they are put on reduction diets belong in this category as do also the obese individuals who develop hypoglycemia six hours after the ingestion of carbohydrate. It is not necessary to postulate an abnormal pancreas in explanation of such cases.

The observation that puppies grow rapidly when injected with extracts of the anterior pituitary that are diabetogenic in adult dogs supports the above. Apparently, in the young dog, the increased demands for insulin consequent to the stimulation of growth, e.g., for nitrogen storage, are adequately compensated by an increased insulin production by the pancreas. Only when the animal has become adult and his total metabolic area accordingly increased, does extra stimulation of insulin demands result in insulin insufficiency and, in the dog, pancreatic exhaustion. In the intact rat, however, pancreatic exhaustion does not ensue upon similar treatment in spite of the fact that all evidence of an increase in insulin production can be demonstrated. That this is probably true for man is indicated by the rarity with which acromegaly is associated with diabetes and by the fact that the pancreas of diabetic acromegals may show signs of increased activity rather than degeneration (28). Similarly, histologic indications of increased Islet activity has been observed in non-diabetic obese subjects (34).

It is of interest to note also that rats made obese in consequence of hypothalamic damage, show first an increase in appetite, followed by an increased intake of food, obesity and eventually transient glycosuria. To our knowledge, pancreatic damage or insufficiency has not been demonstrated in such animals.

In contemplating the reason why obesity so frequently precedes the development of diabetes in man, one must remember that the obesity is due to a relative excessive intake which is in turn preceded by an increase in appetite. Instead of obesity being regarded as an etiologic factor in the genesis of diabetes it is quite possible that it is really that phase of diabetes in which an increased rate of insulin utilization or destruc-

tion is adequately compensated for by the pancreas (i.e., compensated diabetes). In those instances where the rate of insulin utilization continues to be excessive and beyond the capacity of the pancreas to produce insulin, diabetes will become apparent.

When Banting and Best isolated insulin they also discovered that insulin was extremely susceptible to the proteolytic action of trypsin. This was soon confirmed by many investigators and is regarded as the chief reason that insulin is ineffective by mouth. Epstein and Rosenthal (35) reported that trypsin could inactivate insulin without destroying it and presented evidence that the inactivation of insulin could occur "in vivo." Scott repeated some of Epstein's work and pointed out that both destruction and inactivation by trypsin could occur and that the inactivation was an absorption phenomenon. Subsequently it was established that practically all known proteolytic enzymes can destroy insulin.

Studies on the effect of the injection of trypsin and other pancreatic proteinases in animals have not yielded consistent evidence that a diabetic-like state can be induced thereby. Buckley (37) did note that the injection of trypsin in rabbits produced hyperglycemia and inhibited the action of insulin but Weinglass and Tagnon (38) could not demonstrate a similar phenomenon after the injection of chymotrypsin.

Insulin is a protein and is destroyed fairly rapidly after its administration. It is apparent, therefore, that ordinarily insulin is destroyed in the tissues through the action of one or all of the various proteinases which are normal constituents of cells. Hence it is possible that the lack of positive results noted by some investigators after trypsin or chymotrypsin injection may be obviated if some of the intracellular proteinases were administered instead of the pancreatic proteinases.

That proteinases other than trypsin or chymotrypsin may play an important role in carbohydrate metabolism can be inferred from the studies of Cori and Green (39). They demonstrated that phosphorylase, an enzyme which is essential for the formation of glycogen from hexose-1-phosphate exists in two forms; an active form, phosphorylase *a*, and an inactive form, phosphorylase *b*. They demonstrated also that muscle and other tissues contain an enzyme which converts the active phosphorylase *a* to the inactive phosphorylase *b*. This enzyme is referred to as PR enzyme and behaves like a proteinase. They found that when muscle is stimulated the rate of the conversion of phosphorylase *a* is increased indicating an "in vivo" action of the PR enzyme. The effect of such an enzyme would strongly influence the formation and breakdown of glycogen and may have some important relation to the action of insulin.

If it be acknowledged that insulin is destroyed by the tissue proteinases then it would follow that any phenomenon which results in an increase in free proteolytic enzymes would also be associated with an increased destruction of insulin. Further, it would be anticipated that such situations would also be associated with other evidences of increased proteolysis such as

an increase in protein catabolism. That such is the case may be seen in infections, trauma, anoxia, fevers, hyperthyroidism, anterior pituitary treated animals and human diabetics. In all these instances there is both a decreased carbohydrate tolerance, and an increased protein catabolism. Thus, if there is an insulin insufficiency present because of an excessive destruction of insulin, the development of an infection and the consequent release of *more* proteolytic enzymes from injured cells would increase further the rate of insulin destruction and result in what we could call "insulin resistance."

Along such lines was Minkowski's suggestion (40) that diabetic patients do poorly during infection because of an increase in proteolytic enzymes in the blood. Presumably, these enzymes originate in the cells damaged by the infection. Attempts to prove this hypothesis have been made by many workers, some of which demonstrated that blood serum or pus from patients with purulent infections inhibits insulin. Thus, Karelitz (41) observed that normal blood plasma or cells can inhibit insulin, that diabetic blood does so more effectively than does normal blood and that the inhibitory effect is enhanced by the presence of infection. Other investigators have not been able to obtain consistent results.

The administration of anterior pituitary extracts to normal or "pituitary diabetic" dogs results in the development of insulin-insensitivity or resistance. In other words, while the depancreatized dog is relatively sensitive to insulin, the dog in which diabetes is induced by pituitary injections is relatively insensitive. Furthermore, the administration of an anterior pituitary extract to the depancreatized dog also induces an insulin "resistance" in spite of the fact that there is no pancreas that can be impaired further. It has been suggested that these effects of anterior pituitary extracts may be due to the injection of some specific anti-insulin hormone. However it has not been established as yet that such extracts do not contain proteinases which are capable of destroying insulin or that they do not increase the availability of intracellular proteinases in consequence of their ability to induce an augmented protein catabolism in the peripheral tissues (15).

It is true that some investigators have been able to demonstrate anti-insulin substances in the blood of patients with insulin-resistant diabetes, but many more have been unable to do so. Although the effect of anterior pituitary extracts may be due to the presence or formation or specific insulin inhibitors it is possible to explain all the effects of these extracts on the hypothesis that they supply or produce an increased amount of free proteinases which destroys insulin and thereby induces a compensatory increase in insulin production.

It is now fairly well established that insulin is capable of acting as an antigen and can induce the production of insulin-antibodies. Such antibodies have been demonstrated in animals (42) and in some insulin resistant human diabetics (43). Hence it is obvious that an insulin insufficiency may ensue if such antibodies are produced in excessive quantities.

With the preceding, the thesis has been developed that the metabolic syndrome of diabetes mellitus in man is due to an insufficiency of insulin which is due only rarely to a decreased production of insulin by an inadequate pancreas. It is proposed that in most instances of human diabetes there is an increased utilization, destruction or inhibition of insulin by tissue proteinases or insulin antagonists which results in a

decrease in the concentration of circulating insulin. The pancreatic abnormalities noted in some diabetic subjects are attributed in part to insulin insufficiency and in part to those unknown factors which are responsible for the extremely common associated renal and vascular changes. Finally, it is apparent that the cause of diabetes mellitus in man is unknown.

REFERENCES

1. Cawley.
2. Banting, F. G. and Best, C. H., *J. Lab. & Clin. Med.*, 7:251, 1922.
3. Lukens, F. D. W.: *Yale J. Biol. & Med.*, 16:301, 1944.
4. Young, F. G.: *Brit. M. J.*, 2:715, 1944.
5. Mirsky, I. A., Nelson, N., Grayman, I. and Korenberg, M.: *Am. J. Physiol.*, 135:223, 1941.
6. Mirsky, I. A. (in press)
7. Goldner, M. G. and Gomori, G.: *Proc. Amer. Diab. Assoc.*, 4:87, 1944.
8. Homans, J.: *J. Med. Res.*, 30:49, 1914.
9. Allen, F. M.: *J. Metab. Res.*, 1:5, 1922.
10. Copp, E. F. F. and Barclay, A. J.: *J. Metab. Res.*, 4:445, 1923.
11. Bowie, D. J.: *Anat. Rec.*, 29:57, 1924.
12. Haist, R. E.: *Physiol. Rev.*, 24:409, 1944.
13. Mirsky, I. A., Nelson, N., Elgart, S., Grayman, I.: *Science*, 95:583, 1942.
14. Young, F. G.: *Lancet*, 2:372, 1937.
15. Mirsky, I. A.: *Endocrinology*, 25:52, 1939.
16. Lukens, F. D. W., Dohan, P. C. and Wolcott, M. W.: *Endocrinology*, 32:475, 1943.
17. Houssay, B. A., Foglia, V. G., Smyth, F. S., Rietti, C. T. and Houssay, A. B.: *J. Exper. Med.*, 75:547, 1942.
18. Mirsky, I. A., Korenberg, M., Nelson, N. and Nelson, W. E.: *Endocrinology*, 28:358, 1941.
19. Mirsky, I. A., Heiman, J. D. and Broh-Kahn, R. H.: *Am. J. Physiol.*, 118:290, 1937.
20. Warren, J.: *The Pathology of Diabetes Mellitus*, Philadelphia, Lea & Co., 1938; *N. Y. State Med.*, 41:2432, 1941.
21. Gellerstedt, N.: *Beitr. Z. Path. Anat. U. Z. allg. Path.*, 101:1, 1938.
22. Arey, J. B.: *Arch. Path.*, 36:32, 1943.
23. Lapply, T. C., Eitzen, O. and Dutra, F. R.: *Arch. Int. Med.*, 74:354, 1944.
24. Reinecke, A. M.: *Am. J. Physiol.*, 140:276, 1943.
25. Scott, D. A. and Fisher, A. M.: *J. Clin. Invest.*, 17:725, 1938.
26. Joslin, E. P.: *Annals Surg.*, 117:607, 1943.
27. Root, H. F.: *J. A. M. A.*, 127:557, 1945.
28. Moore, R. A.: *Textbook of Pathology*, W. B. Saunders Co., Philadelphia, 1944. p. 1082.
29. Rockey, E. W.: *Ann. Surg.*, 118:603, 1943.
30. Brunschwig, A., quoted by Goldner and Clark (32).
31. Priestley, J. T., Comofort, M. W. and Radcliffe, J.: *Ann. Surg.*, 119:211, 1944.
32. Goldner, M. G. and Clark, D. E.: *Jour. Clin. Endocrinol.*, 4:194, 1944.
33. Greene, J. A., David, A. and Johnston, G.: *Am. J. Physiol.*, 136:595, 1942.
34. Grauer, R. (personal communication).
35. Epstein, A. A. and Rosenthal, N.: *Am. J. Physiol.*, 70:225, 1924; 71:316, 1925.
36. Scott, D. A.: *J. Biol. Chem.*, 63:641, 1925.
37. Buckley, O. B.: *Br. J. Exp. Path.*, 14:57, 1933.
38. Weinlass, A. R. and Tagnon, H. J.: *Am. J. Physiol.*, 143:277, 1945.
39. Cori, G. T. and Green, A. A.: *J. Biol. Chem.*, 151:31, 1944.
40. Minkowski, O.: *Med. Klin.*, 22:437, 1936.
41. Karelitz, S., Cohn, P. and Leader, S. D.: *Arch. Int. Med.*, 45:546, 1930; 45:690, 1930.
42. Wasserman, P., Broh-Kahn, R. H. and Mirsky, I. A.: *J. Immunol.*, 38:213, 1940.
43. Lerman, J.: *Am. J. Med. Sci.*, 207:354, 1944.

Dr. Tolstoi: I regret that I have to terminate Dr. Mirsky's paper, but we still have some very interesting items on the program and we must proceed. Dr. Best's name has been mentioned so often tonight that I want to introduce him to you now and ask him to start the discussion.

Dr. Best: I would like to make a few comments on Professor Peters' presentation and on the papers delivered by Dr. Root and Dr. Mirsky.

Low liver glycogen and excellent combustion of sugar are not incompatible in experimental animals. One of the main actions of insulin when carbohydrate is given in the normal animal is to store glycogen in the muscles. The liver glycogen may be decreased. Diets rich in carbohydrate in the normal animal or similar diets plus insulin in diabetic animals, may produce large depositions of glycogen in the liver without obvious interference with the function of this organ.

In commenting on Dr. Mirsky's paper—it is well known that the starvation treatment used before insulin was available, did prevent coma. Under those circumstances very little fat would be available in the tissues. We know that there is a tremendous rush of fat from the depots to the liver in diabetes. If there is no fat available there will be less ketosis and less tendency to coma. The return of liver fat to the depots when you give insulin to a diabetic animal—the disappearance of the fatty liver—is a striking phenomenon. This is a part of the mechanism by which insulin decreases ketosis.

Some diabetic patients come to autopsy with an atrophied pancreas and very few islet cells. There is good

evidence that under certain circumstances these patients die with very little mechanism left for the production of insulin. We should not lose sight of this fact in spite of the normal appearance of the pancreas in many diabetics.

We know little about the facts of the mechanism of the action of insulin. In the study of the action of most hormones, we find ourselves too near the borderline of our knowledge of chemistry and physiology. With new weapons at hand a great deal more will be learned after the war. There will be a new impetus for medical research.

Dr. Tolstoi: We will now proceed to the questions that have been submitted to the Panel on the Round Table, consisting of the members of the Council of the American Diabetes Association who have had their Council meeting in the City this afternoon. None of these questions have been rehearsed. The experts do not know what they will be called upon to answer. Replies, therefore, are all extemporaneous.

Question No. 1: "In diabetic coma, should insulin be administered intravenously or subcutaneously?"

Dr. Woodyatt: I can't give any specific data on that. Routinely I depend on subcutaneous injection, and in the early days when we compared the two methods of administration, we didn't find any definite advantage in the intravenous method. Perhaps Dr. Best might know more.

Dr. Best: I can speak only as a physiologist. If I had my way, I would give it intravenously as then you are

sure that it will be absorbed completely; this, of course, is not a clinical answer.

Dr. Wilder: I have nothing to add to what has been said. We frequently do when making a salt solution and glucose, add the insulin to what is running through the veins, so often it is given in the vein. If the circulatory picture is very severe, one would turn to the intravenous route; we do so frequently.

Dr. Root: There is a small group of patients with extraordinary subcutaneous atrophy. When insulin was given into the vein, we could obtain a fall in the blood sugar.

Dr. Tolstoi: Question No. 2: "Is the obese mild diabetic difficult to control? Should such patients be given insulin or should they be permitted to be glycosuric?"

Dr. Joslin: Neither. I should send such patients to the minister to learn moral control. We followed a diabetic nun for several years who weighed 259 pounds and had a high blood pressure. In order to profit by a sympathectomy, Dr. Poppen insisted on preliminary weight reduction. She was then operated upon with success, her blood pressure fell from over 250 to 125, her insulin dropped from 64 to 8 units while her weight changed from 259 to 197 pounds.

Dr. Barach: I saw a movie last night called the 'Keys to the Kingdom,' and the priest's advice to an obese woman was "Get thin; the gates of heaven are narrow." In practice I am perfectly willing to go along on a minimum diet without insulin.

Dr. Tolstoi: Question No. 3: What is the maximum dose of regular insulin that can be given at one time? Please explain. Will 100 units be utilized or wasted?

Dr. Best: I am sure that no one here would want to attempt to answer this question. Some would be excreted and wasted. Less effect is secured with high dosages. You more or less have to square the dosage and not double it when you get up to high amounts.

Dr. Beardwood: I think somebody in talking to Abe Lincoln about the length of his legs got the answer from him that they were long enough to reach the ground. I think the dose of insulin should be sufficient to control the blood sugar. You don't get twice as much reduction of the blood sugar from twice as much insulin. When we first begin work on a patient we start out with 30 to 35 units. On the other hand, Snader has followed a patient who for ten months took an average of 1600 units a day and reducing his regular insulin to any great extent resulted in increasing his blood sugar. It is a question of what you want to do.

Dr. Tolstoi: Question No. 4: What is the basis for loss of knee jerks in a diabetic of ten years standing?

Dr. Root: I think this is a question which is difficult to answer. We assume that it is an effect of the diabetes on the nervous system, mainly in the central nervous system, the cord.

Dr. Woodyatt: In the majority of loss of knee jerks in elderly people, it is associated with peripheral multiple neuritis.

Dr. Tolstoi: Question No. 5: What is the explanation, if any, for the cause of death in diabetic coma with no evidence of peripheral failure?

Dr. Mirsky: I wouldn't want to answer that question. If the patient has been in coma long enough, changes occur in the central nervous system. We have a syndrome like traumatic shock.

Dr. Dillon: Years ago our mortality at Philadelphia General Hospital was bad. In one case after another a man's chem. was cured, but after being treated for 12 to 18 hours, he proceeded to die in spite of treatment. In those studies we found that there were certain damages in the brain which we believe to have been the cause of death.

Dr. Striker: I think there are two points that should be stressed when we talk about normal blood chemistry, one is, many of us forget to include nitrogen studies. Kidney damage should be considered. The second point is the use of fluids—normal salt solution; in several instances such hydration was caused that the patient really drowned in his own fluids.

Dr. Tolstoi: Question No. 6: Is it preferable to have high blood sugar in coronary diseases and coronary insufficiency?

Dr. Joslin: It is preferable to have a blood sugar above rather than below in coronary insufficiency. Coronary cases can be treated with insulin to great advantage, but one is never careless, and even an approaching hypoglycemia is avoided. However, what these old arteriosclerotics will tolerate is past belief. A man who had had three cerebral accidents went into diabetic coma and was sent to us with CO_2 . . . and blood sugar . . . milligrams, but during convalescence at one time by error his blood sugar fell to 29 milligrams. However, he suffered no ill effects and was discharged . . . days after entrance.

With regard to diabetic coma: not a word has been said tonight about alkalies; so we are progressing. Insulin should be given and is paramount in treatment. Our series is 603 coma cases since 1923 shows that in the first 50 cases we had 18 per cent mortality and these patients received 83 units in the first three hours; the last . . . cases received 216 units in the same space of time and the mortality was 1.4 per cent. The chief point in the treatment of diabetic coma is to give insulin early and enough of it so that advanced coma never has a chance to develop.

Dr. Tolstoi: I want to express my deep appreciation, and the appreciation of the New York Diabetes Association, to the speakers, Drs. Mirsky, and Peters, and to the members of the Round Table Panel for their participation tonight. I am certain that the audience has profited greatly from the papers and discussions they heard this evening.

The meeting is now adjourned — 11:00 p. m.

Proceedings of the New York Diabetes Association, April 1945

OPEN MEETING

Tuesday, April 24th, 1945, 8:30 p. m.

at

THE NEW YORK ACADEMY OF MEDICINE PROGRAM

Grant P. Pennoyer, M.D., Chairman, Committee on Surgery, presiding

I. PAPERS

1) "SURGERY OF THE ACUTE ABDOMEN IN PATIENTS WITH DIABETES MELLITUS"

Beverly Chew Smith, M.D., Presbyterian Hospital

Discussion: Louis Bauman, M.D., Presbyterian Hospital

2) "RECENT ADVANCES IN THE MANAGEMENT OF GANGRENE AND INFECTIONS IN PATIENTS WITH DIABETES MELLITUS"

Leland S. McKittrick, M.D., Boston, Mass.

II. DIABETES—ROUND TABLE DISCUSSION FROM THE SURGICAL VIEWPOINT

Panel: Frederick M. Allen, M.D., Polyclinic Hospital; Henry Dolger, M.D., Mt. Sinai Hospital; Leland S. McKittrick, M.D., Boston, Mass.; Samuel Silbert, M.D., Mt. Sinai Hospital; Beverly Chew Smith, M.D., Presbyterian Hospital; Samuel Standard, M.D., Bellevue Hospital.

Dr. Pennoyer: It is my pleasure to open this meeting of the Surgical Section of the New York Diabetes Association. It is a great privilege to welcome you all here and I am sure we are going to have a very enlightening meeting. Before the papers are read, I should like to introduce to you the members who constitute the Panel for the Round Table Discussion. Introduced Drs. Allen, Dolger, McKittrick, Silbert, Smith and Standard.

SURGERY OF THE ACUTE ABDOMEN IN PATIENTS WITH DIABETES MELLITUS*

BEVERLY CHEW SMITH, M.D.

IN REALITY, the principles of surgery of the acute abdomen are the same in patients with and without diabetes. However, when the complications of diabetes are coincident with acute abdominal pathology, surgical therapy may best be conservative in the given case. At the outset I desire to express the necessity for close therapeutic cooperation between the surgeon and the physician in any surgery of a diabetic. From experience it has seemed that the constant association between surgeon and physician who have together treated surgical diabetics over a period of time has

made for the more complete therapy in any individual case. The surgeon becomes cognizant of the medical condition and senses the change in the surgical condition as reflected in the patient's response to his medical treatments, and vice versa. If a surgical diabetic is not doing well it is most likely that an inflammatory process somewhere is not completely controlled. Again, as a medical man witnesses improvement in the surgical condition, he almost invariably must modify the intensity of his treatments.

It is estimated that there are six to seven hundred thousand diabetics in the United States and fifty thousand in the Greater Metropolitan area. It is difficult to estimate the number under dietary and insulin treatment and even more difficult to estimate those whose diabetes is controlled because what is meant by controlled diabetes has not been universally agreed upon by those who supervise diabetics. Historically it may be noted in passing that it is rare indeed that a diabetic is operated upon in these times without his diabetes having been discovered. On the other hand, vigilance for this condition is still rewarded by the occasional discovery of a diminished tolerance for carbohydrates with mild hyperglycemia without glycosuria which develops into clinical diabetes following elective surgery, particularly if inflammatory post-operative complications occur. Infection invariably increases the severity of the disease.

The routine history and urinalysis should either suggest further necessary examinations or establish the existence of diabetes. If a glycosuria does not exist, the hyperglycemia, as a rule, is not very high although in the exceptional case, with a high renal threshold, it may be sufficiently high to be of clinical significance.

The acute surgical abdomen may be encountered (1) in those who do not know they have diabetes; (2) in patients who have been treated and considered adequately controlled by their physicians; (3) in persons who are uncooperative and hence their diabetes is only partially controlled, and (4) in a small group of severe cases whose diabetes is so difficult to control that it is rarely completely controlled by diet and insulin over any prolonged period.

The principles involved in the surgical therapy of each of these groups are practically identical, but their application is more one of intensity depending upon the severity and complications in any given case.

After establishing the presence of diabetes, I would list as of major import the following observations: (1) the patient's age, the duration of known diabetes, and an estimation of the time and the degree of its control. Often in the aged, diabetes is not severe and does not present a serious problem of therapy either at, or after operation. Again, it is in the aged whose diabetes has been either partially controlled, or uncontrolled, that

*Published with consent of *New York Medicine*.

we see advanced sclerosis in their peripheral, myocardial, cerebral and renal arteries. These factors may have a very definite bearing on surgical therapy, and the investigation of their extent and severity may require postponement or palliative treatments and the use of many laboratory facilities for evaluation.

(2) The severity of the diabetes and the degree it has modified the patient's metabolism at the time of his admission. Here we resort to blood sugar and CO_2 combining power, and initiate such pre-operative therapy as the degree of hyperglycemia or acidosis may indicate. This may assume such major importance as to require the most expert medical advice and cooperation between the internist and surgeon, as well as their respective house staffs. Whereas it is obviously inadvisable to operate upon a patient in coma, one may in an acute abdominal case be confronted with a patient in coma who cannot be brought out of it until some intraperitoneal inflammatory pathology is relieved. Fortunately this situation is a rarity. It carries a high mortality. Its successful surgical treatment may require more knowledge of principle than dexterity.

(3) Diagnosis — We are justified, if a diagnosis is not obvious, in utilizing as many adjuvant laboratory methods to establish a correct one as is consistent with the patient's condition. This is true in any surgical case, but a correct diagnosis in the presence of a complication such as diabetes will influence such other factors as anesthesia, incisions, duration of procedures and utilization of specific therapies before, at and after operation which may have an early salutary effect.

Appendicitis — Diabetes need not materially affect the surgery of acute appendicitis without peritonitis. The diabetes can be treated during and after operation. The same applies with localized peritonitis without abscess, but hyperglycemia may require more active treatment and a longer time to be controlled. With abscess formation, one must weigh the advantages and disadvantages of appendectomy. If the appendix can be readily removed without further contamination, and the exposure is such that the chances of surgical accidents are minimal, its removal may be justified, but drainage alone of a localized appendix abscess may be, in the presence of a serious complication, a very satisfactory surgical procedure. In a case of diffuse or diffusing peritonitis, diabetes is a serious complication. It affects morbidity, mortality, length of hospitalization and wound healing. Each case should be judged or treated on its own merits.

Acute cholecystitis in a diabetic poses several important and immediate problems. Its early diagnosis may be difficult — a wrong diagnosis and a misplaced incision is a serious mistake. (I recently reviewed three hundred and thirty-one cases of acute cholecystitis operated upon at The Presbyterian Hospital — diabetes occurred in this group 13 times.) Cholecystectomy is the operation of choice in uncomplicated acute cholecystitis without profound pathology elsewhere. The time to operate upon these cases is within forty-eight hours of the onset of the symptoms and/or when the patient is ready for operation. The important point is

whether cholecystostomy or cholecystectomy should be done. The former is simple, requires less anesthesia, smaller incision, less manipulation of inflammatory tissues, is accompanied by fewer post operative complications and is devoid of surgical accidents. The latter is more definitive but more dangerous. In ostomy the removal of the last stone and patency of the cystic duct are of primary importance, but even a mucous fistula may be less serious than accidents associated with ectomy — namely injury to extra hepatic bile ducts, hemorrhage and the spread of infection. In cases requiring common duct drainage with jaundice or inflammation in the head or body of the pancreas — diabetes as a concomitant condition assumes major importance because it becomes difficult to treat, is often exacerbated, has probably caused diffuse changes throughout the vascular system in the age group in which this situation occurs, affects wound healing and prolongs hospitalization.

In peritonitis from perforation of a viscus, closure of the perforation, with or without drainage of the infected peritoneal areas, is the decision of the moment. The decision to drain depends upon the time between the perforation and the operation, the degree and extent of contamination or infection, the presence of foreign bodies or necrotic tissues and uncontrollable hemorrhage. The skin and subcutaneous wounds may best be left open. Penicillin or sulfonamide drugs locally and systemically may be indicated depending upon the organisms present. Prolonging operating time because of technical considerations of unimportant details is unwarranted, particularly if any degree of shock develops. Wound closure should be rapid and secure, possibly with through and through wire or heavy silk sutures. If time permits the peritoneum may be closed separately to avoid gut being extruded against or between the through and through sutures. As a rule if closure of the perforation occludes the lumen of the gastro intestinal tract, it is best to perform a side tracking operation rather than a major resection.

Incisions: Incisions should be properly placed and no larger than necessary. Any incision can be enlarged but no incision can be decreased in its extent. This is an unscientific admonition bordering on censure, but its repeated encounter warrants emphasis.

The McBurney muscle splitting incision has re-established itself as the one of choice in lesions of the appendix and variations from it must be justified. Its enlargement by a so-called Weir extension into the sheathes of the rectus with medial retraction of this muscle provides adequate local and pelvic exposure without excessive peritoneal contamination.

In perforations of the pyloric region, either duodenal or gastric, a small transverse incision lateral to the right rectus muscle through the obliques and transversalis in the direction of their fibers, without incising or dividing the right rectus muscle, gives an excellent exposure and adequate space to close the perforation. It can be enlarged transversely as necessary. Its closure is usually easier than a split or retracted right rectus incision. Wound separation with evisceration is

much less frequent and early ambulation is possible with less chance of wound weakness.

For extensive exploration or resection of the small or large intestines a transverse incision across one or both recti is preferable to other types of incisions, unless it is specifically contraindicated.

In uninfected wounds, sutures of silk, cotton or steel wire are preferable to cat gut. If silk is used in contaminated or infected wounds, it is advisable to leave the skin and subcutaneous tissues open and lightly packed with a silk or gauze tampon.

Drainage: Drainage when indicated should be adequate, maintained in position as placed at operation, and removed thoughtfully as the clinical evidence warrants. Inasmuch as infection seems protracted by hyperglycemia, adequate drainage of the intraperitoneal site and layers of the abdominal wall must be carefully considered. The indications for drainage of the peritoneal cavity in the presence of acute pathology are the same as in non-diabetics, but when the dilemma of to drain or not to drain in the diabetic occurs, I believe it is safer to drain. The effect of chemotherapy upon such situations is mentioned elsewhere. It is true that in the abdomen where blood supply is adequate, hyperglycemia and the chemical metabolic imbalance frequently associated with it may affect inflammation and its repair less than in extremities, but the consequences of the spread of infection within the peritoneal cavity are still serious.

Drains should be brought out through the most direct route, but if a counter wound is used, the abdominal wall wound may still require drainage by being left open through the subcutaneous tissue.

Silk or rubber tampon types of drains may provide a very adequate outlet but when withdrawn may leave a wound weakness and, when in situ, evisceration may occur around them. Rubber tubing should be soft, have an adequate lumen without a thick rigid wall; its intraperitoneal end should be bevelled; one or more openings can be made near its end and a gauze tape may be placed in it to protrude against a bleeding area and to maintain its patency. It should not rest upon anastomose, sutured areas, large blood vessels or a distended viscus. This gauze wick is usually withdrawn the first or second post-operative day, the tube gently lifted and returned near its original site, and gentle irrigation with a small amount of warm saline usually brings away old blood or exudate. The tube end outside of the abdomen should be flush with the abdominal wall with a safety pin traversing its wall without crossing its lumen. The dressing should not press upon it, be secure, adequate to collect exudate, comfortable and should not restrict respiration.

A cigarette or Penrose tube drain, when used alone, should be watched for retention of exudate. The late withdrawal of such a drain should be gradual if the tract is deep and exudate is present. If withdrawn too fast or too soon accumulation of exudate may persist in the bottom of the tract. A catheter or small tube may have to be inserted immediately upon withdrawal of this type of drain to preserve the entire tract, or that

portion of the tract through the abdominal wall may have to be maintained longer by a small tube.

Chemotherapy: Diabetes has no known effect upon sulfonamide or penicillin or vice versa. The dosage of each is the same as in non-diabetics, and the same complications may occur with the sulfonamides locally and systemically so that the same safe-guards should be taken when they are given. Sulfonamides have been used so universally of late as local applications, more instances of sensitization to these drugs are being encountered when therapeutic doses become necessary. All organisms should be tested for sensitivity to penicillin. The effect of both of these substances has been as brilliant when properly used against sensitive bacteria as in the non-diabetic group. If one general statement could be made concerning the effect of these agents upon the acute abdomen in the diabetic, I should say they have increased the extent of local operability when combined with adequate and sound surgical principles, and have decreased post-operative and wound complications in possibly an even greater degree in this group of patients who are somewhat more susceptible to infection. These substances are more effective when given systemically in infected areas which have an adequate blood supply.

Carcinomas of the gastro-intestinal tract rarely present acute symptoms unless they perforate, bleed or obstruct. Their elective excision with restoration of continuity in diabetics is a major procedure, before which every preparatory therapy should be even more meticulously carried out than in the non-diabetic. These include adequate blood, serum protein, hydration, decompression and cleansing of the entire bowel, pre-operative preparation with a sulfonamide systemically or in the bowel lumen, penicillin intramuscularly and the use of a Miller-Abbott or Wangenstein tube for decompression. The duration of the operation, extent of tissue exposure and repair, increases the difficulty in controlling the blood sugar post-operatively, and such other local complications which may even further exacerbate hyperglycemia.

In conclusion, may I again state that the degree of combined medical and surgical supervision of these cases will almost certainly reflect in the morbidity and mortality statistics of any institution.

From the Department of Surgery, College of Physicians and Surgeons, Columbia University, New York City.

Dr. Pennoyer: I am glad now to call on Dr. Louis Bauman of the Presbyterian Hospital.

MEDICAL MANAGEMENT OF THE DIABETIC PATIENT DURING AN ACUTE ABDOMINAL EMERGENCY

LOUIS BAUMAN, M.D.

WHILE WE STRIVE to keep the urine sugar free and the blood sugar normal in uncomplicated diabetes, this becomes difficult or impossible when an acute abdominal condition is superimposed. Alarming acidosis with lowered sodium bicarbonate in plasma and acetic acid in the urine is rarely encountered in the surgical wards of the Presbyterian Hospital. In 25

years less than five such cases have presented themselves. In such a situation the surgeon may delay the operation until sufficient insulin, salt solution and sodium bicarbonate have been administered to insure glucose oxidation, and restore water and electrolytes to the plasma. Sterile sodium bicarbonate solution is now available in ampoules, and if its injection is controlled by blood determinations, it is a useful therapeutic agent in this condition. Fortunately, acidosis is rare and the parenteral administration of glucose, salt and insulin is the chief concern of the medical attendant after an abdominal operation. Unless fluids are tolerated by mouth, about 1500 cc. of 5% glucose in saline is usually given intravenously or subcutaneously twice during the 24 hours. Before each infusion 10 units of insulin are injected. The urine is tested about every three hours (catheterization may be necessary),

and 10 units of standard insulin are injected for 3+ or 4+ glucose reaction and 5 units for less. As soon as nausea and distension have subsided, peroral fluids, such as sweetened tea, ginger ale and bouillon, are given, and this is followed by a gradual return to the solid diet and resumption of the single dose of depot insulin. Complications as infection with fever, distention, nausea and vomiting may compel modification of the above plan. More assiduous attention may be necessary in very severe cases of diabetes. The danger of adding insulin shock to the burdens of the operated patient must always be borne in mind.

The self explanatory tables (following) to be shown on the screen include the data on a case of acute cholecystitis and acute appendicitis complicated by diabetes.

DIABETIC CHART U.H.696248						
DATE	TIME	CHO GMS.	INSULIN UNITS	URINE SUGARS	REMARKS	
12/25	11:30 AM	50 clysis 5% glucose	15 S		Orders: 15 units S. insulin for 4+ sugar, 10 units S insulin for 3+ sugar	
	7:30 PM	100 " " "	15 S			
	8:15 PM		15 S			
	11:00 PM		15 S			
12/24	9:30 AM		10 S	3+		
	5:00 PM		25 S			
	8:00 PM		15 S	4+		
12/25	7:00 AM	2000 cc. saline infusion		0		
	11:00 AM			+		
	1:00 PM			+		
	3:00 PM			+		
	7:00 PM			+		
	10:30 PM			+		
12/26	1:00 AM	25 clysis	5 S		Operation lasting 2 hours	
	2:00 AM			+		
	10:00 AM	75 "	15 S			
12/27	7:30 PM	100 "	10 S	3+		
	5:45 AM			+		
	10:00 AM	100 "	20 S		Allow broth, tea and ginger ale	
	12:00 M		10 S	3+		
12/28	1:00 PM			2+		
	2:00 AM			+		
12/29	6:45 AM			+		
	1:45 PM	50 "	15 S			
12/30	11:30 AM	50 "	15 S			
12/31	3:00 AM			+		
	3:10 PM	50 "	15 S		Reg. 100-60-50 diet	
1/2	9:45 AM		15 PZI		Reg. 100-80-50 diet	
1/5	6:30 AM		15 PZI	0		
1/7	6:30 AM		20 PZI	0	Blood sugars - 144 and 156	
1/12	6:30 AM		25 PZI	+		
1/13	6:30 AM		25 PZI	+		
1/18	6:30 AM		25 PZI		Blood sugar - 127	
1/19	6:30 AM		25 PZI		" " 90, 97	

Woman, aged 65, admitted on December 23, 1942, with typical history of acute cholecystitis, fever, and jaundice. W. B. C. 20,200, bile, sugar and albumin in the urine. Liver enlarged, tenderness over gall bladder region. Serum bilirubin 6.4; blood sugar 331; CO₂, 47.5; phosphatase 7.4. No diacetic in urine. At operation December 26th, cholecystectomy and removal of stone in common bile duct was carried out.

DIABETIC CHART (U.H.#510008)

Severe diabetic boy (Age 15 yr.) developed acute appendicitis.
Operated Sept. 22, 1940 at midnight.

DATE	TIME	CHO gms.	PROT.	FAT	INSULIN	URINE BLOOD		REMARKS
						SUGARS	SUGARS	
9/23	6:15 AM	0	0	0	10 St.	4+	215	Only saline p.r. or hypo.
	2:30 PM	0	0	0	10 St.	4+		
	2:50 PM	0	0	0	15 St.		265	
	5:30 PM	0	0	0	20 St.			
9/24	6:15 AM	100	50	50	10 St.	4+		
		fluids p.o.			25 Globin			
	11:25 AM				10 St.	4+	175	
	3:30 PM				10 St.	4+		
	4:45 PM				15 St.	3+	185	
	9:00 PM				15 St.	2+		
9/25	11:30 PM				5 St.	+		
	6:45 AM	150	70	50	25 Glob.	±	164	
		soft and fluid diet						
	2:30 PM					+		
9/26	3:00 PM					4+		
	7:00				15 St.		180	
	9:00 AM	150	70	50	70 Gl.	±	120	
		Regular diet						
9/27	2:30 PM					±		
	3:00 PM					0	102	
	7:00 PM					0		
	9:00 PM				15 St.	3+		
9/28	9:00 AM				80 Glob.	0	72	
	2:30 PM					+		
	3:00 PM					0		
	7:00 PM					0	63	
9/28	6:00 AM					0		

Dr. Pennoyer: I should like now to present to you Dr. Leland S. McKittrick of Boston who will speak on

RECENT ADVANCES IN THE MANAGEMENT OF GANGRENE AND INFECTIONS IN PATIENTS WITH DIABETES MELLITUS

LELAND S. MCKITTRICK, M.D.

IT IS A GREAT pleasure to be here this evening but I am not too sure that I have a great deal to impart. In the management of patients suffering from diabetic gangrene it has seemed to us that if we could eliminate infection and if we could think and act only in terms of the circulatory problems, we could manage this group of patients possibly in quite a different way than what we have been accustomed to do under the existing conditions. We all know that, given a patient even with normal circulation, infection may cause thrombosis in the smaller or even larger vessels and necrosis. If the patient has diminished arterial supply and has diabetes, too, then we have a more complicated problem still.

In reviewing some of our past experiences, we found in 1934 that one half of the patients that we lost after operation on the lower extremities, were lost because of infection, either local or general, which we were unable to control. We suggested then that if we could eliminate infection it ought to be possible and practical to do surgery including major amputations on these patients with diabetes with a mortality rate of approximately five per cent. This five per cent of patients die from cardiovascular and other conditions independent of infection. It seemed plausible then that we might

get our mortality below five per cent if we could eliminate infection and that this should be our goal.

Table I shows the mortality ratio from 1941 to 1944 after major amputations. Infection as a major problem has been largely eliminated in the management of this group of patients. It is doubtful if we can expect materially to lessen the death rate in this group. Now that we have penicillin and the other chemotherapeutic agents the question arises: Can we lessen the number of major amputations done with equal safety to the patient?

TABLE I
New England Deaconess Hospital
Amputations Through or Above Mid Lower Leg
1941 to 1944 Inclusive

YEAR	MAJOR AMPUTATIONS	DEATHS
1941	42	1
1942	46	4
1943	44	0
1944	37	2
Totals	169	7 = 4.1%

During the past two years — using penicillin preparation for, during and after operation — we have been doing an increasing number of amputations through the foot, just proximal to the heads of the metatarsals. In most instances the operation is done for conditions which in the past we have felt obliged to do an amputation through or above the mid lower leg. We are not as yet in a position to say too much about the end results. The wounds heal nicely. (See Figures 1 and 2.) The patients walk well by merely stuffing the end

of the shoes with lambs wool. This group will be reported later when we can be more certain of the indications and end results. Table II shows the number of different operations done last year.

TABLE II
Operations 1944

New England Deaconess Hospital

Level of Amputation	No.	Deaths
Through or above mid lower leg	37	3
Transmetatarsal	13	0
One or more toes	64	1
	114	4 = 3.5%



Figure 1A—Male diabetic, seventy-five years of age, with gangrene of entire fourth toe. No palpable pulsations below the popliteal artery. Bed rest; penicillin, 100,000 units daily for ten days, in preparation for transmetatarsal amputation, and continued for ten days after operation.

Another procedure which we have been using now for the past three years is the partial closure of wounds following removal of one or more toes proximal to the heads of the metatarsals for infection. Although we began doing this before chemotherapy was available, these agents have undoubtedly widely extended the usefulness and safety of the operation. (See Figures 2 and 3.) Not only does this partial closure result in better scars, but the time saved in hospital days runs into many weeks on a single case.



Figure 1B—Wound ten days following operation. This patient last seen four months after operation with an excellent anatomical and functional result.

I wish to say a few words about carbuncles. About six months ago I was asked to see a 45 year old male diabetic, a patient of Dr. Joslin. He had a rapid pulse, high fever, chills and fever, no pus in his neck and no evidence of localization, but a firm diffuse spreading carbuncular type of infection. Blood culture was positive for staphylococcus aureus. He was given 100,000 units of penicillin a day. In four days his temperature was normal and he left the hospital ten days later with a soft flaccid neck without having had any operation.

A few days later I was asked to see a man my assistant had scheduled for operation. He was seventy, fat, his diabetes uncontrolled. The process extended from one side of the neck to the other. There was no localization but a typical early carbuncle. I cancelled his operation because I was afraid to operate on him at that time. We started him on penicillin, giving him 100,000 units a day, and that man left the hospital about two or three weeks later after complete subsidence of the inflammatory process.

I don't want to give any false impressions. I don't want to leave you with the impression that the treatment of carbuncles is by penicillin at the exclusion of surgery. Many, probably most, will still require sur-



Figures 2A and 2B—Sixty-year-old male diabetic with osteomyelitis of fourth and fifth metatarsals and involvement of tarso-metatarsal joint. Treatment: Penicillin, 100,000 units daily for five days, fol-

gery. I have every expectation, however, that penicillin, used early and intelligently, may completely alter our present concept of this serious complication.

In conclusion: Careful selection of time and type of operation combined with the use of our present chemotherapeutic agents have been important factors in eliminating infection as a cause of death after operations on the lower extremities.

Amputation through the foot just proximal to the heads of the metatarsals has been successful in a number of cases which in previous years would have been subjected to amputation at a higher level. Increasing evidence suggests that this operation should and will be done with increasing frequency.

Partial closure of the distal portion of wounds following excision of a toe with the head of its metatarsal in the presence of infection has proven safe, shortened the period of hospital stay and given better end results.

Early and active use of penicillin in carbuncles and other staphylococcus skin infections may completely

lowed by transmetatarsal amputation with curettage of tarso-metatarsal joint. The tibial one-third of the wound was closed with cotton skin sutures, and the remainder packed loosely with dry gauze.

alter our present concept of the management of these cases.

Dr. Pennoyer: I think your opening remarks, Dr. McKittrick, that you have brought very little for us were very inappropriate—I think you brought a great deal. I hope many more will be encouraged to try local surgery on these feet and try to duplicate your results.

I shall leave the discussion of Dr. McKittrick's paper to be part of the panel.

The first question isn't really a surgical question but we have medical men on this panel, so I shall ask Dr. Bauman to answer this inquiry:

"What do you consider the proper control of a diabetic patient?"

Dr. Bauman: May I answer this question by describing the treatment of a new diabetic patient. The diet is appropriate for the nutritive state of the patient—if underweight, a high calorie diet, if of normal weight, a maintenance diet, and if overweight, a low calorie diet is ordered. For example, a recent arrival, a lad under 15, six feet and one inch tall, weighed 145 pounds. He is receiving 350 carbohydrate, 100 protein, and 210 fat, that is about 3700 calories, and 150 units of globin insulin one hour before breakfast. This maintains the urine

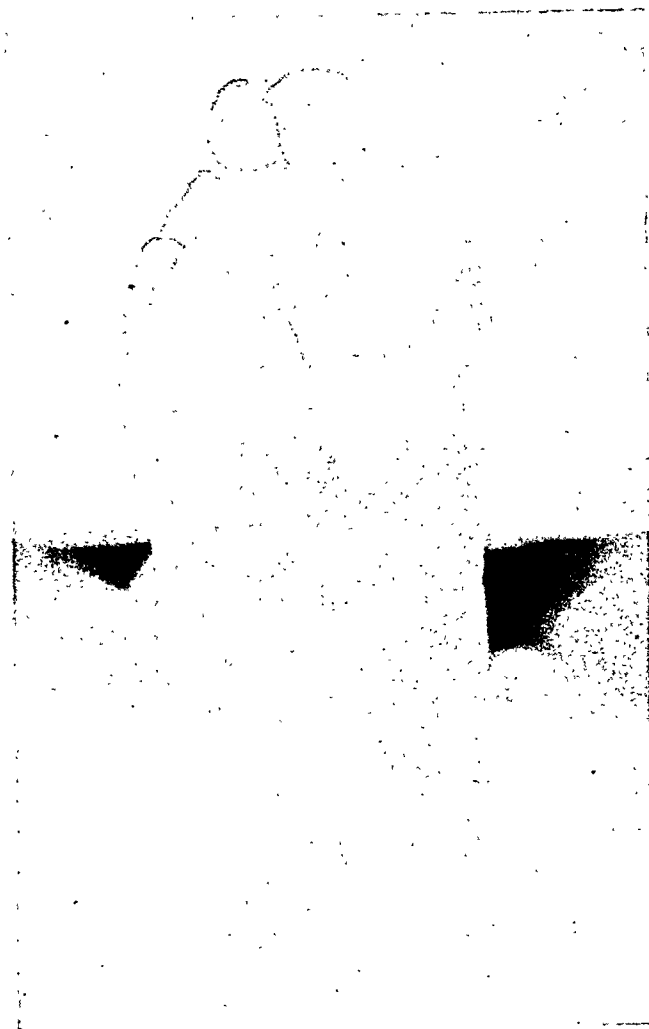
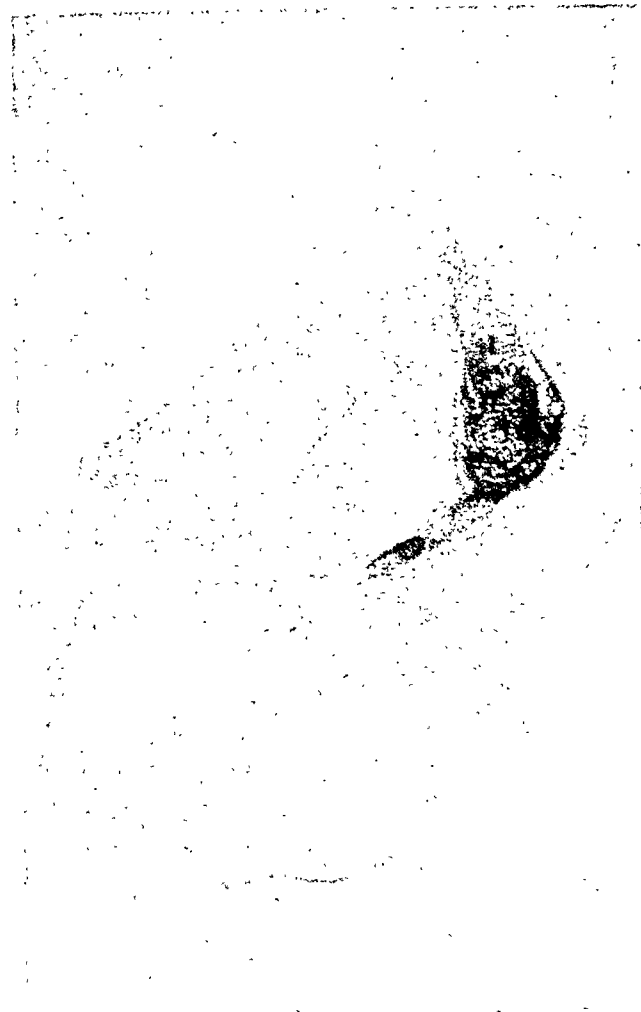


Figure 2C—Same as 2A and 2B. Three weeks after operation. Wound is clean and ready for pinch grafts. Wound completely healed ten days later.

sugar free throughout the 24 hours and keeps the blood sugars normal. We think the principle employed in determining the diet is sound and simple and easily grasped by the medical student.

One dose of depot insulin is preferred, except in older people suffering from advanced coronary or cerebral arteriosclerosis who receive two doses of standard insulin to avoid the danger of insulin shock.

We insist on sugar free urines and normal blood sugars. In our diabetic clinic, two-thirds of the patients have normal blood sugars. We are deeply conscious of the likelihood of retinal and early peripheral arteriosclerosis in neglected cases.

Dr. Pennoyer: I shall call on Dr. Dolger to express his opinions.

Dr. Dolger: I was sorry to hear this question—re proper control of a diabetic patient—as it is an old warhorse. There are two things about control. We are afraid of insulin shock regardless of the age of the patient. With activity a low blood sugar may result without a change in diet or insulin dosage despite a previous hyperglycemia. It is a different story when the patient is in bed. Frequent shocks do occur in some patients and there are many factors to be considered—emotional state, activity, etc. We consider it to be good control if the patient maintains weight, is free of acetone and is devoid of symptoms such as polyuria, etc. If a patient

takes insulin we can disregard the glycosuria. We are inclined today to give more liberal carbohydrate diets, and not try to maintain a normal blood sugar level.

Dr. Pennoyer: The second question: "How do you select the site of amputation in diabetic gangrene and why?" I should like to present Dr. Silbert.

Dr. Silbert: I would like to answer the second part of the question first. There are three good reasons for doing a low amputation: 1) the mortality is very much lower. I don't know what type of amputation Dr. McKittrick's figures represent, but surely in New York the mortality for thigh amputations has been appallingly high. I collected published reports on thigh amputations in diabetics from several of the larger hospitals and in 637 thigh amputations the mortality, with 300 deaths, was 47 per cent. Individual hospitals reported figures of 25 per cent to 35 per cent. In recent years I have done amputations below the knee and can report that with 92 diabetics amputated through the leg there were six deaths, or 7 per cent mortality. So you see, one of the advantages in doing amputations below the knee is the lower mortality. 2) This type of operation saves the function of the knee joint. Many of these patients are 60 to 70 years old and such patients find it very difficult to use an artificial leg on a thigh stump. Only 50 per cent of the men and very few of the women do get about. If the knee joint is saved, the patient can steady him-



Figures 3A and 3B—The third right toe with the head of its metatarsal has been removed for a deep penetrating ulcer by taking out a wedge of tissue. The distal two-thirds of the wound has been closed with interrupted cotton. The proximal third in the sole of the foot was packed loosely with dry gauze. Complete healing in four weeks.

self, and function is greatly improved. Many get accustomed to the use of artificial legs and use them well. 3) This type of operation leaves a stump that is practically always painless. All sorts of operations and resections are done for painful stumps left by thigh amputations. It has been my experience that leg stumps are never persistently painful.

These are three good reasons for doing the low amputation. The advantages are so great that we have tried it in practically every case. In the 92 cases mentioned only five had to be re-amputated because of poor healing. In the first operations a tourniquet was used and it was chiefly in these cases that re-amputation was required. Since we have stopped using a tourniquet, we have had very little trouble with healing.

Amputations were done below the knee regardless of whether the femoral and popliteal arteries were open or closed. Unless the closure has been very recent, sufficient collateral circulation may be expected below the knee for satisfactory healing.

Dr. Pennoyer: I have several questions here that I should like to have answered by Dr. McKittrick: 1) "What is your experience with local application of penicillin in these cases?" 2) "Where can we get more details on the transmetatarsal amputation?" 3) "Have you tried refrigeration anesthesia in any of these cases?"

Dr. McKittrick: We have had relatively little experience with the use of penicillin locally in our diabetic cases. Possibly because we have not used it properly, we have not been impressed with the results obtained in those cases in which it has been used.

As regards additional information on transmetatarsal amputation, I have not yet had opportunity to study the literature to see what already has been written on this procedure. I doubt very much that it has been used to any extent in the group of patients that we are discussing today. What I have said tonight is simply an endeavor to bring you up to date on the way we are thinking and what we are doing at the present time. We have been doing these operations over too short a period of time for us to have had sufficient experience to warrant any definite conclusions. Later on we hope to review in detail this group of cases.

I am glad that the question on refrigeration anesthesia is worded as it is, since I would prefer not to go into a discussion of this question this evening. We have not used refrigeration anesthesia in any of these cases. Our experience with spinal anesthesia, using about seventy-five milligrams of procaine, has been extremely satisfactory. It has proven safe, and that it is easily given is shown by the fact that our inexperienced resident staff, after a short period of instruction, give most of our anesthetics for these operations.

Dr. Pennoyer: I should like to ask Dr. Allen to express his opinion on refrigeration.

Dr. Allen: You would expect my opinion to be favorable. One definite fact is that refrigeration lowered the mortality of amputations in City Hospital. I believe all surgeons will agree that in the average public charity hospital of a large city with unselected cases, it is impossible to reach any such low mortality figures as Dr. McKittrick gives. The entire staff of independent surgeons at City Hospital agreed on the marked reduction of mortality. I question whether Dr. McKittrick or anybody else could improve on their results, with this material, and if he were working with such cases, I believe he would use refrigeration. It should be mentioned that our figures include our entire mortality from all causes, and the deaths from strict cardiovascular causes, often occurring weeks after the operation, are more numerous than Dr. McKittrick's total mortality. Furthermore, I have a clear personal recollection of the time when surgeons used to examine some of my diabetic gangrene cases and decline to operate. That was the main reason for the research which developed the refrigeration method, and one result of that method is that the inoperable cases are now all operated upon, frequently with excellent results as the reports from numerous surgeons testify.

Theoretically, injurious effects are imputed to either the tourniquet or the low temperature. In the long series at City Hospital, even with the most extremely sclerotic arteries, there has not been a single instance of thrombosis or other harm attributable to the tourniquet. This record is confirmed by all surgeons who have had most experience with the method, and the recovery of animals' legs after as long as 54 hours of ligation should be a sufficient demonstration of the protection which cold affords against tourniquet pressure. The supposition of injury from cold can be answered in two ways, according as circulation is present or absent. With circulation retained, there are reports by Mock, Grossman, Nachlas and others of good operative healing in legs which had been packed in ice for two weeks or longer. With circulation absent, there are the above-mentioned records of ligated legs kept safely in ice water for 54 hours, and the report of Blakemore and Lord who cut off dogs' legs, stored them in refrigeration for 24 hours, and obtained

healing after suturing them back in place. It is noteworthy that the imaginary objections to this method are raised by persons who have never tried it or whose experience has been insufficient to develop a trustworthy technique, while surgeons from all parts of the world who have given the procedure a fair trial have thus far endorsed it without a single exception. The greatest advantage obviously is the unique avoidance of shock, as well as the other disasters which are well known to have occurred with every other mode of anesthesia. While every other anesthesia, including spinal anesthesia, can dangerously add to shock, neither these nor local nerve block can in the least degree inhibit shock. This strictly physiological and harmless inhibition of shock is the essential reason for the spectacular benefit from refrigeration anesthesia in poor-risk patients and the improved nutrition and healing and avoidance of complications are contributory.

Dr. Pennoyer: I would like to ask Dr. Standard to express his opinions on this subject of refrigeration.

Dr. Standard: The use of cold for the control of infection owes its origin in part to the establishment of our understanding of the dangers of the application of heat to infections of the lower extremities with vascular inadequacy. The danger of the use of heat lies in its raising the metabolic rate of the tissues involved without at the same time assuring an increase in blood supply to meet the increased requirements.

In following the logic of this thought to its ultimate application, one arrived at the opposite end of the problem. The question arose as to whether a) the application of cold would lower the metabolic rate to the low level commensurate with its existing vascular supply and so inhibit further breakdown; and b) whether the lowering of temperature would inhibit activity of invading organisms and thus lower infectious activity and spread.

Although once the method is used there can be no positive clinical control with which to compare its effectiveness, it is generally acceded that the application of cold to a foot with a cellulitis does reduce the active inflammation locally and often results in systemic events such as fall in temperature and reduction in general toxemia. The temperature reduction is often dramatic, falling four to five degrees in as many hours. The term toxemia is vague but broadly speaking includes the improvement in the general well being of the patient both subjectively and objectively.

Refrigeration, by the above effect would seem to offer an advantage as a temporary measure in preparing a toxic, febrile patient for surgery.

Two other claims have been made for the method: 1) Refrigeration may so localize an otherwise spreading lesion as to permit local surgery in patients that might otherwise have required major (above or below knee) amputation. 2) It may permit localization with spontaneous amputation thus avoiding surgery altogether. Such outcome has been seen to occur in limbs treated by the usual so-called conservative methods without refrigeration. To date there is no statistical evidence to support the assumption that refrigeration will result in a greater number of such results than can be achieved by the usual, non-refrigeration methods. Dr. Allen's published statement bears this out. He states, "the question whether a sclerotic limb which needs amputation can be saved by reduced temperature must at present be answered in the negative."

The final use of refrigeration, and one that seems to us separate and apart from the claimed effectiveness in controlling infection, is its introduction as a method of anesthesia for major amputation. For effective anesthesia refrigeration must be combined with the use of

a tourniquet above the site of amputation. To those of us who have enjoyed the advantages of a good anesthesia service with the variety of inhalation, regional and intravenous methods, the use of refrigeration as an anesthetic measure is a throwback to the days of ethyl chloride freezing for surgical procedures. It is distinctly a step backwards.

On the Third Surgical Division at Bellevue Hospital we have had no post-operative death directly attributable to the anesthesia, and none in which it contributed significantly to post-operative morbidity or mortality. Dr. McKittrick reported a series of cases tonight of major (mostly above knee) amputations with a mortality of four per cent. Neither refrigeration nor a tourniquet was used in this series. Low spinal anesthesia was used in all cases.

As for the effectiveness of cold in controlling infection in the stump above the knee, a large enough series of cases without refrigeration have been published of primary closure without drainage even in the most badly infected feet. These have healed by primary union proving the absence of infection in the stumps.

The use of tourniquets was discarded years ago. To endow it with special virtues when combined with freezing seems illogical. It is locally injurious to tissue immediately under it, to the sclerotic vessels which it compresses and creates anoxia to tissues distal to it for a matter of hours. The anoxia it induces is complete; the lowering of the metabolic activity of the tissues as a result of freezing is incomplete; the tissue must suffer from the relative anoxia it imposes upon them and to that extent the tissues are injured.

Our present technique of gentle surgery in amputations cannot be carried out with frozen tissue. The meticulous hemostasis which requires clamping each vessel and only the vessel with a minimum of adjacent tissue is difficult with frozen tissue and unsatisfactory with the tourniquet in place until some time after amputation.

In our opinion refrigeration has no place as an anesthetic agent. The tourniquet is an added danger. Refrigeration is a form of injury. Its advantages and possible dangers require further study and evaluation.

Dr. Pennoyer: I have several more questions for Dr. McKittrick: 1) "What about the injection of penicillin locally in carbuncle areas?" 2) "What type of anesthesia do you think optimal on metatarsal operations?"

Dr. McKittrick: I believe that the local injection of penicillin in and around carbuncles has appeared in the literature. We have had no experience with it. I do not see how it can fail to be painful, and it is difficult for me to believe that it is completely devoid of hazard.

As suggested above, we have used low spinal anesthesia for all of our transmetatarsal amputations.

Dr. Pennoyer: The next question will be the final one for this evening, and I should like to ask Dr. Standard to answer the following: "Does forced protein feeding play any part in preparing the patient for surgery?"

Dr. Standard: The answer to this question does not apply strictly to the diabetic patient, but since it is an important preoperative measure in all surgical cases, its effect becomes more important in a group of diabetic patients who may reach surgery with greater nutritional deficiencies than the non-diabetic group of cases.

The importance of adequate protein replacement was first emphasized by Dr. Ravdin and his co-workers in their experimental and clinical investigation. It was through their work that our error in the establishment of the physiological function of the liver was brought to the attention of the surgeon. They proved that a lipid laden liver was more vulnerable to the usual liver poisons than a normal liver and added the therapeutic dictum

that proteins are more important in reducing liver lipids than carbohydrates. The previous effectiveness of carbohydrate administration can be explained on the basis of its protein sparing effect. For adequate re-proteinization, the patient must be given a sufficient nitrogen intake to replace loss and to furnish material for the current catabolism of native protein. Added to this protein intake, there must be a source of carbohydrate sufficient to meet the caloric needs of the patient. If the diet is not calorically adequate in carbohydrates, the proteins will be burned as fuel and not utilized for replacement. Dr. CoTui in the experimental laboratory of the Third (New York University) Surgical Division at Bellevue Hospital has shown the importance of adequate nitrogen administration in the healing of decubitus ulcers as well as surgical wounds. The material used has been a mixture of amino acids under the trade name of *Amigen*. There are other mixtures available on the market that are probably equally effective. The quantitative administration of nitrogen has been based on the following plan. The daily excretion of nitrogen is 10-15 grams. The administration has consisted of $\frac{1}{2}$ gram of

nitrogen per kilogram of body weight and the administration of carbohydrates on the basis of 40-50 calories per kilogram of body weight. Powdered *Amigen* is 12% nitrogen and each gram of *Amigen* furnishes 3.4 calories.

An example of a clinical case of a man weighing 65 kilograms would be as follows: At $\frac{1}{2}$ gram per kilogram it would mean 30 grams of nitrogen or approximately 250 grams of powdered *Amigen*. To this is added 500 grams of dextri-maltose, the total being dissolved in 1000 cc. of water. The patient is fed 200 cc. of this mixture five times a day. This is fed entirely by mouth whenever the gastro-intestinal tract can be used. This gives a total of about 3000 calories a day and is sufficient in itself to meet the caloric requirements of the patient. Vitamins B and C and liver extract parenterally are added to this. One of the great drawbacks to the use of *Amigen* is its unpalatableness. The addition of chocolate flavor is often preferred by patients having to take *Amigen* by mouth.

Dr. Penneyer: This meeting is now declared adjourned -- 10:30 p. m. Thank you all for coming.

Proceedings of the New York Diabetes Association, January, 1946

2 East 103rd Street, New York 29, N. Y.

OPEN MEETING

Under Auspices of the Committee on Internal Medicine
Saturday, January 26, 1946, 8:30 p. m.

at

THE NEW YORK ACADEMY OF MEDICINE PROGRAM

Edward Tolstoi, M.D., Chairman, Committee on Internal Medicine, presiding

I. A QUARTER OF A CENTURY IN MEDICAL RESEARCH

Charles H. Best, C.B.E., F.R.S.

Director, Department of Physiology and Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

II. CARBOHYDRATE METABOLISM IN TRAUMATIC SHOCK

R. E. Haist, M.D., Ph.D.

Associate Professor of Physiology, University of Toronto, Toronto, Canada

III. FACTORS AFFECTING FAT TRANSPORT IN THE ANIMAL BODY

Charles H. Best, C.B.E., F.R.S.

Director, Department of Physiology and Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada

The meeting of the New York Diabetes Association, Inc., held at the New York Academy of Medicine, New York City, on Saturday, January 26, 1946, convened at 8:40 p. m., Dr. Edward Tolstoi, Chairman, Committee on Internal Medicine, presiding.

Chairman Tolstoi: Will the meeting please come to order?

I have two very pleasant duties this evening. The first is to welcome the Council of the American Diabetes Association to this meeting.

The Council met here today and our meeting was planned in a way to coincide with the time of their meeting, so we could have them here with us this evening.

My second pleasant duty is to preside over this meeting. Most of you have programs and you see that we have turned the meeting over almost entirely to the Department of Physiology of the University of Toronto.

The speakers certainly do not require much of an introduction. They are known to you. You have seen both of them. You have known them by reputation, and Dr. Best, the man who will speak first, has been on this platform a number of times, and we have always enjoyed him.

I take great pleasure in introducing Dr. Best to you, who will speak on "A Quarter of A Century in Medical Research." Dr. Best is Director of the Department of Physiology and the Banting and Best Department of Medical Research, University of Toronto, Toronto, Canada.

Dr. Best!

A QUARTER OF A CENTURY IN MEDICAL RESEARCH

C. H. BEST, C.B.E., F.R.S.

Director of the Department of Physiology and of the Banting and Best Department of Medical Research, University of Toronto.

MORE RESEARCH is needed to determine the point in a person's career at which he should be permitted to "reminisce." In submitting a title for this very informal talk before the New York Diabetes Association I had in mind that it will soon be twenty-five years since we first had insulin available. Twenty-four years ago this month the first injection was given to a diabetic patient in Toronto.

The years have passed very rapidly since the autumn of 1920 when I received an appointment in Professor J. J. R. Macleod's department and began work on a

problem in carbohydrate metabolism. It is quite possible that one of the reasons for my interest in diabetes was the fact that I had vivid recollection of the two years when my father conducted a small private hospital in Eastport, Maine. He began his medical course at Dalhousie University, Halifax, Nova Scotia, and completed it here in New York City. He spent most of his forty-five years of active practice in Pembroke, Maine, where I was born. As I remember it, he was the mainstay of the medical staff of this little hospital in Eastport and the only trained nurse was my father's sister, who was at that time a severe diabetic. This aunt, Annie Best, like many other Nova Scotian girls, had gone to the Massachusetts General Hospital to train as a nurse. Dr. Elliott Joslin was a houseman in the M. G. H. at that time and when my aunt, some years after the completion of her nursing course, developed diabetes, she renewed his acquaintance and became patient No. 875 in his records. I can remember clearly the meals which she prepared for herself and her efforts to adhere strictly to her diet and to carry out her nursing duties. Her life was prolonged by undernutrition and a low carbohydrate intake but she died of diabetes some years before insulin was available. I can remember other medical cases because I gave anesthetics under my father's direction when I was in my early teens, but none made an impression comparable to that of diabetes in our own family connection.

The research problem which I attacked during my Fifth Year in the University of Toronto (1920), in collaboration with E. C. Noble, was an extension of the famous piqure experiments of Claude Bernard. We mastered the technique of producing piqure diabetes and became familiar with many of the accepted chemical methods used at that time in the study of the diabetic organism. Our program was to interfere with each, in turn, of the various nerve pathways by which the needle hole in the medulla might cause the liver to discharge an unusual amount of sugar into the blood stream. No report was made of our preliminary results but they were recorded very carefully in a notebook--the same one incidentally which Banting and I subsequently used.

In the autumn of 1920 I had decided, after consultation with several University professors (particularly with Professor R. B. Thompson, who has mentioned the matter many times in the subsequent years) that I would spend a second year in research in Professor Macleod's department and would attempt to obtain an M.A. degree in Physiology. When Professor Macleod, in April 1921, outlined Banting's working hypothesis to Noble and to me and asked us if we wished to collaborate with him, I was very anxious to do so. Professor Macleod could not arrange for any stipend or living expenses. I had enough saved from post-discharge pay received in 1919, to carry on for a time and later in the summer of 1921, I borrowed money from Banting. My father would gladly have provided the amount which I needed but a general practitioner in a small town has many uses for the fraction of his

earnings which he actually collects. Noble was also interested in the new problem but he was tired after a strenuous year and as his father had a country place near Toronto it was arranged that I should carry on the necessary chemical work alone for a time and that he would return after six weeks. He did so, but as only one person was needed for the chemical aspects of the work it was decided without argument that I would carry on. The myth that we had tossed a coin to decide who should work first with Banting and that Noble did not return to the laboratory as we had arranged, originated in the fertile mind of a newspaper reporter who published it in the daily press. Unfortunately Banting subsequently referred to this mythical episode as if it were true, but, as Noble and I who were the only ones present at the time agree, it has no basis in fact. (Dr. Noble subsequently collaborated in many important aspects of the insulin work. He has had a distinguished career in this last war as Senior Medical Officer overseas with the Royal Canadian Air Force.)

I have written many times of Banting's brilliant initiation and vigorous leadership in the insulin investigation. In discussing my own part in the isolation of insulin I have no claims to make which have not already been definitely staked out for me by Fred Banting. He has correctly stated that we began work in partnership and that some of the useful ideas in the early development were mine. Our collaboration began on May 16th, 1921. This date was set because I finished my final examination for a B.A. degree in Physiology and Biochemistry on May 15th, 1921. Banting's initial hypothesis was of course invaluable. The formation of it was responsible for the start of the work. The scientific basis of the hypothesis was challenged by other workers soon after our first paper appeared. If one were particularly interested, the application to degenerated and intact pancreas under identical conditions, of the extraction procedure we originally used, would give interesting results. However these might turn out, the paramount value of Banting's idea would still exist and I can think of few others which have so completely fulfilled their purpose. It was my great good fortune and unique privilege to work in partnership with Canada's greatest scientist, in the friendliest relationship, before he became famous.

Banting has described, on many occasions, the various stages in the development of the insulin researches. Many of the productive ideas were "children of his brain." He was well trained in surgery but had little knowledge of the chemical methods involved in the study of metabolic problems. The surgical procedures were entirely new to me. We began working up the necessary surgical and chemical techniques. Professor Macleod advised certain procedures, some of which were useful, while some led to difficulties. The two-stage operation for pancreatectomy gave us a good deal of trouble, probably because it was difficult to maintain asepsis under our working conditions. In spite of this I had the greatest difficulty in persuading

Banting to change to the single-stage method. The D/N ratio in urine was, however, the real stumbling block. My figures never showed the 3.65 which Professor Macleod insisted we must get in completely depancreatized animals before giving our pancreatic extracts. The ratios were variable and almost always much lower than 3.65. Banting doubted the accuracy of my results but I was sure of them. I looked up the literature and almost convinced Banting that the high ratio was only obtainable in phlorrhizin diabetic dogs — which is of course the case. We eventually decided to pay little attention to the D/N ratio.

Both Banting and I have written of our difficulty in interrupting the pancreatic ducts when we tied them with catgut. This simple problem appeared important at the time when we were anxious to push ahead rapidly. We were fortunate in deciding to extract the degenerated pancreas after seven weeks because the insulin content of pancreas decreases after duct ligation and if we had waited for a longer interval we would have had less insulin available. Insulin was, of course, extracted in very definite amounts from degenerated pancreas and Banting and I visualized herds of cattle whose pancreatic ducts had been tied. We worked out our simple extraction procedure together. I was responsible for the addition of the small amount of acid which we used. This was added in an effort to secure the same pH as the tissues in which we felt the anti-diabetic hormone must function. It is to be regretted that we were so afraid of a departure from the physiological range of hydrogen ion concentration. If we had used strong acid, many of our early difficulties would have been avoided. If, however, we had used strong alkali we would have been in real trouble because, as you know, insulin is destroyed rapidly in alkaline solution.

The use of foetal pancreas resulted from discussions Banting and I had during several night sessions in the laboratory. The decision to collect and utilize this material was Banting's. The use of alcohol in the extraction of whole pancreas has an interesting history. It was, of course, obvious but perhaps not so apparent then as it would be now. When these experiments were initiated I thought that I had hit upon a very good idea. My friend and classmate, Henry Borsook, now of the California Institute of Technology, helped me determine the concentration of alcohol necessary to precipitate pancreatic proteolytic enzymes. I can still visualize Banting when he saw the results of the alcoholic extracts of whole pancreas. He said: "Do you know, Charley, I believe that Professor Macleod said something about using alcohol as a precipitating agent for proteolytic enzymes." Various incorrect accounts have been given about this phase of our work by people who certainly had no first-hand knowledge of the situation.

The first report of our work on the antidiabetic hormone was made by Banting and myself at the Physiological Journal Club on November 14, 1921. The first report outside Toronto was before the American Physiological Society at the New Haven Meeting in De-

cember, 1921. As Banting and I were not members, Professor Macleod's name was added. His name, however, did not appear on the two more detailed papers which were published in the *Journal of Laboratory and Clinical Medicine* in February and May, 1922, and which described our work from the beginning up to that time. Banting enjoyed making charts but not writing papers. I have the originals of the charts for those papers which he made, with the exception of one, which I gave to Dr. Joslin. I probably destroyed the manuscripts of these first detailed scientific papers which I had written.

When Banting and I decided to make an extract for administration to a human diabetic it was agreed that I should secure a beef pancreas aseptically and work up the material as carefully as possible to avoid bacterial contamination. I confess that I have always been pleased that I had the privilege of making this material. With the help of a worker in the abattoir I opened a likely looking steer and removed the pancreas with sterile instruments. When the final extract was ready I gave it to a diabetic dog and secured a good fall in blood sugar. Banting injected the material under his own skin and then under mine. We waited twenty-four hours and as only a mild local reaction developed we decided to take samples to the General Hospital. A friend of Banting's and of mine, Dr. Ed. Jeffery, gave the first injection to Dr. Walter Campbell's patient, Leonard Thompson, the first human diabetic to receive insulin. A great deal of interesting data could be collected on the first patients to receive insulin in various countries. The first in the United States was a patient of Dr. John R. Williams of Rochester.

Just how many diabetics in this country now require insulin is difficult to estimate. The demand for insulin has increased at a much more rapid rate than we expected. The total distribution in this country has doubled every four or five years for the past fifteen years.

It is quite possible that further reminiscences about the early days of insulin would tire you and my title indicates that twenty-five years of research work is to be discussed. As a matter of fact, work on insulin has proceeded almost without interruption in my laboratory. The last war did interrupt the series of studies on insulin content of pancreas in which Dr. R. E. Haist and I were intensely interested. These findings were reviewed by Dr. Haist last year in *Physiological Reviews*. The further work of Dr. D. A. Scott and Dr. A. L. Fisher, on protamine zinc insulin, in the division of the Connaught Laboratories for which I was then responsible, was also discontinued during the war.

In 1925 when I went to work in England with Sir Henry Dale, who was then Director of the National Institute for Medical Research in London, I had decided to work on any problem except insulin. (Actually I returned to this field after six or seven months). I was very much interested in the vasodilator factors in certain tissues — particularly liver. Physiological tests indicated that histamine was one of the active

factors and Sir Henry was very pleased to return to a field in which he had for many years been keenly interested. It was, of course, one of the many to which he had made fundamental contributions. In the course of our investigations histamine was for the first time isolated in crystalline form from normal animal tissue. The key collaborator in this aspect of our studies was the late Harold Ward Dudley. We found large amounts of choline in the tissue extracts and this was also isolated in pure form, but this was not the first time that choline had been isolated. At that time I reported from Dale's laboratory, an interesting synergistic relationship between the vasodilator effects of histamine and choline.

I became very interested in the possibility that histamine might be formed in the body from histidine and as the lung appeared to be particularly rich in histamine I used that tissue in the search for a decarboxylating enzyme. I found no formation of histamine but a rapid disappearance of both the naturally occurring base and of added histamine. This disappearance of histamine appeared to be enzymic in nature and further evidence of this was subsequently obtained when I returned to Toronto. The enzyme system was named histaminase and many studies have now been made on it. My collaborators and I tried very hard to demonstrate an action of injected histaminase in the intact animal but obtained little or no evidence in favour of this action. This did not prevent certain commercial firms from marketing a product of questionable potency and even more dubious efficacy. Histaminase is a fascinating enzyme system which may be of considerable clinical interest, but it has not as yet, and is unlikely to have, an established therapeutic role.

In the work on histamine and histaminase we used a great deal of heparin. It was then available only in very crude form and I decided to organize a group with the objective of improving the material. Dr. A. F. Charles and Dr. Scott some years later, isolated heparin in crystalline form. In the course of this work they developed a method now widely used for the preparation of very potent heparin.

The availability of adequate amounts of pure heparin enabled us to carry out several series of experiments on the prevention of thrombus formation. Some of you may have seen the films we made to demonstrate this process. In the presence of heparin, thrombus formation may be completely prevented. The first extensive clinical studies using heparin were made by our collaborator in the experimental work, Dr. Gordon Murray of the Department of Surgery, University of Toronto, and solutions of purified heparin have since been extensively used in vascular surgery. My colleagues Dr. E. T. Waters and Dr. L. B. Jaques, isolated heparin in crystalline form from the blood of dogs in anaphylactic shock.

The causative agent of a certain haemorrhagic disease of cattle is contained in spoiled sweet clover hay. This was first shown by Dr. Schofield of the Ontario Agricultural College, University of Toronto. You are all familiar with the brilliant work of Dr. Link and his collaborators in isolating and synthesizing dicou-

arin. This substance and heparin are now both used in the prevention of thrombosis. Dicoumarin can be given orally but there is a latent period of many hours before it is effective. Heparin is not effective by the oral route but when given intravenously exerts its effect promptly. Heparin is of great *physiological* significance and the members of my group — particularly Dr. Jaques — have been investigating it continuously since we have had it available in pure form. Jaques has found an enzyme — heparinase — which inactivates heparin. Heparin is neutralized almost instantaneously by the intravenous administration of protamine, as Chargaff originally showed.

In 1928 I became very much interested again in fatty livers in diabetic animals. Banting and I had planned in 1922 a series of long continued observations on diabetic dogs treated with insulin. We were unable to carry out this work because Banting undertook for a time the clinical treatment of diabetes and I was forced to return to the preparation of insulin. Allan and others under Professor Macleod's direction, however, carried out these studies and found a type of fatty liver not due to lack of insulin but preventable by some component or components of beef pancreas. I am not going to review the history of what I have called lipotropic factors here. Dr. J. M. Hershey made a great forward step when he found that crude lecithin could be substituted for beef pancreas. Professor Macleod was not convinced that the crude lecithin was not exerting its effect by supplying one of the well known dietary factors and advised me, when I succeeded him, to supervise the work very carefully before it was reported from the department. As you know, this turned out to be a very novel and interesting study, and choline, betaine and a component of casein (later shown by Tucker and Eckstein to be methionine), were identified in our laboratories as lipotropic factors.

During the period 1930-1939 results in three fields of research were published from our laboratories. The new field of the effects of diets on insulin content of pancreas was developed by Dr. Haist and myself. The effect of diet and insulin on the prevention of diabetes in dogs was explored. The heparin studies and those on the lipotropic factors were pushed forward as vigorously as possible with the help of junior and a few more senior workers. Perhaps we would have been better advised to concentrate on only one field. It would have been less entertaining, and one has a right to some entertainment when medical research is an avocation as well as a profession.

This work and pleasure was interrupted for us, as for so many others, in 1939. Most of the problems I have mentioned were dropped immediately. In September, 1939, with the invaluable help of my friend Dr. William Thalhimer of New York, my colleagues and I organized the Canadian Dried Serum Project which after some vicissitudes grew very rapidly. Over 2,000,000 donations of blood were secured by the Canadian Red Cross, dried in the Connaught Laboratories and the University of Montreal, and made available to the Canadian armed forces overseas and to ci-

vilian and military authorities in England.

During the winter of 1940-1941 many members of my research group joined me in forming the Medical Research Division of the Royal Canadian Navy. It was a privilege to be a part of the organization which grew during the war from a strength of less than 2,000 to 100,000 and which was responsible for conveying approximately half of all supplies shipped from North America to the British Isles. We even helped to guard the coast of the U. S. A. in the winter of 1941-1942. The results of our medical research in the Navy are being reported in a special number of the *Journal of the Canadian Medical Services*.

With the cessation of hostilities our minds have turned again to peace time problems. What we trust will be an active and productive group is being rebuilt for the continued studies of carbohydrate metabolism, the lipotropic factors, blood clotting and thrombosis, and several new ventures. Research of all kinds is receiving more attention than ever before in its history and we are engaged in Canada, as you are in the United States, in attempting to make adequate provision for its freedom, maintenance and direction.

Chairman Tolstoi: I am going to ask the one man who I think is entitled to discuss this paper probably more than any one in the audience if he will. I am sure all of you will guess who that man is. Dr. Joslin, won't you be good enough to say a word or two?

Dr. Elliott P. Joslin: Ladies and Gentlemen, and Dr. Tolstoi, thank you very much for the privilege of coming down here tonight, but I will not take the time to discuss the paper, and I am sure I should not do that.

I was only too glad to have an opportunity to be here. Thank you for calling on me. (Applause)

Chairman Tolstoi: Dr. R. E. Haist, Associate Professor of Physiology, of the University of Toronto, will make the second presentation.

The title of his paper is "Carbohydrate Metabolism in Traumatic Shock."

CARBOHYDRATE METABOLISM IN TRAUMATIC SHOCK

R. E. HAIST, M.D., Ph.D.

THERE ARE MANY varied changes in shock secondary to injury. Of these, the changes in carbohydrate metabolism especially merit the attention of anyone interested in diabetes. We should like to know first, the nature of the changes that occur in the animals in shock and secondly, whether or not these changes can be related in any way to diabetes. I may say at the start that there is more information about the changes in carbohydrate metabolism in shock than there is concerning any relation of secondary shock to diabetes.

Shock may result from burns, haemorrhage, trauma, or anoxia of the extremities produced by tourniquets or pressure cuffs. The work of our group was confined to a study of the changes in animals whose hind limbs had been made anoxic by the application of pressure cuffs. Most of the discussion will be concerned with this type of shock, and will deal with studies con-

ducted in large part by my colleagues, J. I. Hamilton, E. J. Pugh, M. A. Ashworth and E. S. Goranson. It may be well at the start to indicate briefly the general procedure used for inducing shock in dogs and rats in these experiments.

In dogs, pneumatic cuffs were applied to the hind limbs, inflated to a pressure greater than arterial blood pressure and left in position for 5 to 6 hours. On release of the cuffs the limbs became swollen and the animals developed signs of shock (1).

In rats, the procedure was similar except that special metal clamps were used instead of the pneumatic cuffs. These clamps were left in place for 12 to 14 hours and then removed. After removal of the clamps the limbs became swollen and the animals developed signs of shock (2). The animals were kept at a constant environmental temperature (27° C.) throughout the experiment.

It is interesting to note at this point that many of the shocked rats survived when the injured limbs were reclamped, i.e., when narrow clamps were placed high on the legs after the swelling was practically complete. The average survival time for untreated shocked rats was 3 hours and 12 minutes with the mode between 2 and 2½ hours. When the shocked rats were re-clamped 1 hour after the first removal, 41 out of 48 survived. When the shocked rats were re-clamped 2 hours after the first removal, 40 out of 60 survived (2). Measurements of limb volume carried out many hours after reapplication of the clamps showed that the limb volumes were not appreciably reduced after re-clamping. The fluid trapped in the injured, re-clamped limbs is lost to the body, yet the animals recover.

We shall see later that some of the metabolic changes occurring in shock are rather quickly reversed by this re-clamping procedure. It is known that re-clamping improves the peripheral blood flow in shocked animals, but the manner in which it brings about its effect is still a matter of debate.

We have described the methods of inducing shock in our experimental animals. Now let us consider the changes in carbohydrate metabolism.

The blood sugar changes in heart blood from fasting rats were consistent. It was found 1) that the blood sugar level rises as a result of the clamping procedure, 2) that the level is still further increased early in shock, and 3) that terminally the concentration of sugar in the blood is reduced again and may even fall below the control values.

It would appear from the work of others (3) that the elevation in blood sugar while the clamps are in place may be ascribed to sympathetic stimulation as a result of pressure exerted by the clamps on underlying nerves. There is also good reason to believe that the increase following the release of the clamps is due to the liberation of adrenaline (3, 4). The hypoglycemia that occurs later in shock probably depends on several factors; 1) a depletion of stores of glycogen in the liver, 2) a failure of the new formation of sugar in the liver, 3) an increased utilization of glucose by peripheral tissues.

As evidence for the increased use of glucose by peripheral tissues, Russell, Long and Engel (5) present the finding that in the eviscerated (or liverless) rat the blood sugar falls more rapidly after haemorrhage than in control animals, that is, the sugar is removed more rapidly by peripheral tissues in the shocked animal.

In our experiments with rats, then, the blood sugar levels increased after the clamps were applied. After the clamps were removed and shock was developing, this blood sugar level rose still higher. Finally, later in the course of the development of shock a reduction in blood sugar and even definite hypoglycemia was evident.

Associated with these changes in blood sugar were alterations in carbohydrate stores. There was, for example, a reduction in the glycogen concentration of liver in shocked rats as compared to fasting controls or rats with clamps remaining in position. In specially treated rats with higher initial glycogen values the difference is more pronounced. In the shocked animals, too, the glycogen content of skeletal muscle is considerably reduced (6). In the injured extremities, i.e., the ones to which the clamps had been applied for 12 to 14 hours, the glycogen concentration in most instances was not measurable. However, the muscles of the forelimbs, which were uninjured, exhibited a definite reduction in glycogen content also. The controls showed an average value of 0.38 g.% while in the shocked rats the concentration was 0.19 g.%. Since in the shocked rats the stores of carbohydrate in liver and muscle are reduced, while at the same time the blood sugar level falls below that of control animals, it seems likely that either more sugar has been utilized peripherally or else the new formation of carbohydrate from non-carbohydrate sources has been reduced.

In addition to these changes in the level of blood sugar and the reduction of carbohydrate stores, the shocked animals also show an altered response to glucose. Following glucose administration by stomach tube there is a high and prolonged increase in blood sugar level. Not only are the blood sugar values higher than those of the clamped control animals, but also they are not reduced four hours after the sugar is given.

Some equally definite results were obtained after the intravenous injection of glucose in dogs. Repeated intravenous tests were undertaken in which one half gram of glucose per kilo was injected every half hour, the blood sugar sample being taken just prior to each injection. In control dogs there was an initial elevation in blood sugar, returning towards the normal again after several hours, i.e., the Staub-Traugott effect was evident. In the shocked animals the blood sugar level showed a progressive increase to very high values. Twenty-four hours later, if the animal survived, the sugar was often still above the normal fasting level. The length of the period of cuff application influenced the tolerance. If this were four hours or less, the tolerance change usually was slight. As a rule, five hours application was necessary for a good effect (7).

An attempt was made in both intact and partially

depancreatized animals to induce permanent damage to the pancreatic islets by successive periods of shock, during which the blood sugar was maintained at high levels by glucose injection. Difficulty was encountered in this attempt, since a lesser degree of injury failed to produce the tolerance change and an injury sufficiently severe to cause the changes in tolerance usually killed the animal. Under the circumstances the study of whether or not permanent diabetes could be produced by repeated injuries of this type with high prolonged blood sugar levels was rather unsatisfactory.

Using transfusions to promote survival in partially depancreatized animals, it was hoped that there might be some indication of diabetes of a persistent type. So far there has been no evidence in the animals that survived that a persistent glycosuria or elevated fasting blood sugar level resulted from this procedure. While these experiments are not satisfactory as yet, we may say, however, that injuries of the type we have described gave rise to marked changes in carbohydrate tolerance; that unless the period of anoxia was longer than 4 hours the tolerance changes were not great; that if the periods of anoxia were much longer than this the tolerance changes were very marked, but the animals usually died. Transfused animals that survived showed no persistent glycosuria.

While the changes in blood sugar level following glucose administration in shocked rats and dogs are definite, perhaps the most outstanding difference between the control and shocked animals is shown in their ability to store glycogen in the liver. Glucose was given by stomach tube at the time the clamps were removed and the glycogen content of liver was studied at 4 hours later. Four hours after the glucose was given, 20 control rats showed an average liver glycogen value of 1.16 g. %, whereas at the same time a similar group of shocked rats gave an average value for liver glycogen of 0.093 g. %. This difference between shocked and control rats is not due to the clamping itself, since rats having the clamps left in place responded much like the control animals (2). The impaired storage of glycogen in the liver is evident earlier in shock as well. When the determinations were made two hours after the glucose was given, i.e., two hours after the clamps were removed, a similar difference between the "shock" and control groups was found ("Shock" average, 0.56 g. %; control average, 0.84 g. %). This indicates that the impairment in the storage of glycogen in the liver is not merely a terminal event in shock. It will be evident from what has been said that rats in shock exhibit an impaired ability to store glycogen in the liver when sugar is fed. This change occurs only after the clamps are removed and is not due to the clamping procedure itself.

Was the poor storage of liver glycogen due to a defective absorption of glucose? Tests of the absorption of glucose from the gastro-intestinal tract indicated that at four hours after glucose administration by stomach tube, the residue of reducing substances in the gut was much the same in the control and "shock" groups. Practically all the glucose had been absorbed

by that time. The actual rate of absorption of glucose was not measured. While it has been reported that the rate of absorption of sugar is reduced in shock, it seems unlikely that poor absorption of glucose from the gut has anything to do with the reduced glycogen storage in the livers of these animals, since this reduced storage occurred despite the fact that the blood sugar level was very high.

The reclamping procedure which, you will recall, leads to survival, rather quickly brings back the ability of the animal to store glycogen in the liver. The restoration would seem to be more rapid, the earlier the clamps are reapplied (2).

In view of the great change in the response to glucose it seemed desirable to find whether or not other sugars were similarly affected. In control unshocked rats the administration of fructose gave rise to as great if not a greater increase in liver glycogen than did glucose. When fructose was given to the shocked rats the storage of glycogen in the liver was no better than when glucose was administered. A point of interest, however, is that the transformation of fructose to glucose can still take place in the shocked rats. In shocked rats given fructose, the blood glucose level was elevated. This elevation was as marked as in clamped control animals. The blood fructose level showed little change. In fact, the levels of blood glucose following fructose administration were similar to those found when glucose itself was given to the shocked rats. It would seem then that the ability of the rat to transform fructose to glucose is not greatly impaired in shock (7).

Because of the high blood sugar levels and the low liver glycogen in the shocked rats given glucose, it was desirable to try the effect of insulin injection in these animals. Two units of insulin were injected subcutaneously into shocked rats given glucose. Insulin administration did not enhance the storage of glycogen in the liver—one probably would not expect it to—but it did lead to a very definite reduction in the blood sugar level below that of the shocked rats. The administration of insulin along with glucose also delayed the fall in the glycogen of the uninjured muscles in shocked rats, but the reduction was usually evident later. A good part of this retarding effect may be due to the glucose itself.

It seems likely from these results that in the shocked rats given glucose the fall in blood sugar level following insulin administration is not due to any enhanced storage of sugar as glycogen in the liver and muscles. Since insulin caused a marked reduction in blood sugar in these animals yet did not improve the muscle glycogen, one is tempted to conclude that the insulin produced its effect by stimulating the direct utilization of glucose in peripheral tissues.

The shocked rats, then, are unable to store glycogen after glucose, and have a decidedly abnormal sugar tolerance. Insulin does not improve the glycogen storage in the liver, does not prevent the fall in muscle glycogen, but does lower the blood sugar level.

What is the cause of these altered responses to car-

bohydrate? One of the first things that comes to mind is tissue anoxia. A number of observers have found that exposure of rats to low oxygen atmospheres gives changes in carbohydrate rather similar to those observed in shock. Hyperglycaemia followed by hypoglycaemia has been reported, the hypoglycaemia as in shock apparently being associated with an increased rate of removal of sugar by peripheral tissues (8).

In our experiments it was found that sufficiently severe anoxia prevented the storage of liver glycogen after glucose was given. The rats kept in low oxygen atmospheres and given glucose had a concentration of liver glycogen less than $\frac{1}{8}$ that of controls.

Engel, Harrison and Long have shown that anoxia of the liver can give rise to certain biochemical changes similar to those obtained in shock. We have confirmed the finding of these and other workers that the oxygen supply to liver is reduced in shock. The flow of blood in the portal vein becomes slower, and the calculated oxygen saturation and oxygen content of portal vein blood is diminished. It would appear, then, that anoxia can produce certain metabolic changes similar to those observed in shock and it also seems evident that in some situations in the body there is a diminished oxygen supply. Whether or not the diminution is sufficiently great to produce the metabolic effects has not been established in our experiments. Pure oxygen under pressure will not lengthen survival or improve glycogen storage in the shocked animals. This is not an argument against anoxia as an important factor in shock. It would hardly be expected that increased oxygen supply would greatly improve the condition in the animal if the anoxia results from an altered circulation, or from some derangement of tissues preventing the use of oxygen.

Some have suggested that in shock, metabolism in peripheral tissues is of the anaerobic type. This seems to be so. Since the anaerobic breakdown of carbohydrate yields much less energy than when it is metabolized aerobically, more carbohydrate is required. This has been offered as an explanation of the increased peripheral utilization of glucose in the shocked animals. Other evidence for anaerobic metabolism is the reduction in muscle glycogen previously mentioned, the increase in blood lactate and a marked fall in body temperature and limb temperature.

Some work done with Dr. K. C. Fisher indicates that there is a rapid fall in body temperature and in foreleg temperature in rats after the removal of the clamps. I should like to call attention to the fact that in our experiments certain major metabolic changes occur almost immediately after removal of the clamps. This is indicated by the precipitous fall in body temperature and foreleg temperature. Many contend, with good reason, that adrenaline liberation occurs early in shock. It should be noted, however, that if that is so the calorogenic effect of adrenaline is not evident in these animals, and also its effect on heart rate is absent.

When the injured limbs are reclamped and the animals survive, the temperature ceases to fall and starts to rise again. This indicates that the general metabolic

changes are stopped and even reversed by the reclamping procedure.

It has been suggested that a depletion of high energy phosphorus compounds, essential for the metabolism of carbohydrate, is a major factor in the development of shock. In experiments with E. S. Goranson it was found that while the muscle of the clamped legs contained little or no adenosine triphosphate and phosphocreatine, the uninjured muscles of the forelimbs contained amounts of these materials not greatly different from that of controls. The turnover rates of adenosine triphosphate and phosphocreatine, estimated by the use of radioactive phosphorus, also were not greatly altered. At this stage in shock, then, i.e. $2\frac{1}{2}$ hours after the clamps were removed, there was no appreciable reduction in these high energy phosphorus compounds either in concentrations or in turnover, except in the damaged limbs. This is at a time when changes in glycogen storage are occurring and when the body temperature and limb temperatures are rapidly falling. Under the circumstances, it is hard to credit the reduction in high energy phosphorus with a major rôle in shock.

We have shown that in our experiments the shocked

animals exhibit marked changes in blood sugar level and carbohydrate stores; that they have an abnormal tolerance for administered glucose and fail to store glycogen in a normal fashion in liver and muscle; that insulin lowers the blood sugar in these animals but does not increase muscle or liver glycogen; that fructose can still be transformed to glucose and that the concentrations and turnover of adenosine triphosphate and phosphocreatine are not reduced at a time that many of these changes occur and when the body temperature is falling. Since most of these changes can be rather quickly reversed by reclamping, it seems evident that a change occurring in the damaged (and anoxic) tissues of the shocked rats is affecting the activity of parts remote from the site of the injury. This effect appears to be due to causes other than loss of fluid from blood vessels.

So far we have been unable to establish any relationship between the type of injury we have described and diabetes. However, in animals not previously diabetic, the changes in carbohydrate metabolism are very profound and provide some promising leads for further investigation.

REFERENCES

1. Hamilton, J. I. and Haist, R. E.: *Can. J. Research*, 23:89, 1945.
2. Haist, R. E. and Hamilton, J. I.: *J. Physiol.*, 102:471, 1944.
3. Mylon, E. and Winternitz, M. C.: *Am. J. Physiol.*, 144:494, 1945.
4. Engel, F. L., Winton, M. G. and Long, C. N. H.: *J. Exper. Med.*, 77:397, 1943.
5. Russell, J. A., Long, C. N. H. and Engel, F. L.: *J. Exper. Med.*, 79:1, 1944.
6. Hamilton, J. I. and Haist, R. E.: Unpublished data.
7. Pugh, E. J. and Haist, R. E.: Unpublished data.
8. Gregoire, F., Leblond, C. P. and Robillard, E.: *J. Aviation Med.*, 15:158, 1944.

Chairman Tolstoi: This very interesting paper is open for discussion.

Dr. Mirsky!

Dr. Mirsky: I just want to compliment Dr. Haist on a beautiful piece of work, which I am sure when continued will be most productive, not only from the point of view of shock but as some of you are aware, I think, from the point of view of the genesis of diabetes as such, since I personally believe the same mechanisms are involved there.

Chairman Tolstoi: Dr. Dock, would you like to comment?

....There was no response....

Chairman Tolstoi: Would anyone else like to comment?

....There was no response....

Chairman Tolstoi: Before going on with the program, I should like to call on Dr. Louis Bauman for an important announcement.

Dr. Bauman, won't you come up here, sir, please?

Dr. Louis Bauman: Ladies and Gentlemen, it has been the policy of the Clinical Society of the New York Diabetes Association to elect members, out-of-town members, who are distinguished for their work in this field to Honorary Fellowship.

It gives me great pleasure to present this certificate to Dr. Best. (Applause)

Would Dr. Joslin please come up?

I am very glad to present this to you as the foremost

clinician in your field, and to Dr. Best I should say as one of the greatest human benefactors.

..Certificates of Honorary Fellowship were presented to Dr. Joslin and Dr. Best, amid applause..

Chairman Tolstoi: The final paper on the program will be given by a member of the New York Diabetes Association, Dr. Charles Best.

Dr. Charles H. Best: Mr. Chairman, Ladies and Gentlemen, I thank you most sincerely for this honor. Perhaps it justifies speaking of twenty-five years in medical research to receive honors of this kind, an evidence that perhaps you have reached the peak of your career and can begin to reminisce.

FACTORS AFFECTING FAT TRANSPORT IN THE ANIMAL BODY

C. H. BEST, C.B.E., F.R.S.

Director of the Department of Physiology and of the Banting and Best Department of Medical Research, University of Toronto.

I MAY summarize briefly what I wish to discuss during the next half hour, in the following way. Our knowledge of fat digestion and absorption has not greatly increased during recent years. We know, unfortunately, only a little more about the mechanism by which fat is carried in the blood or in other fluid tissues. We have gained, however, an entirely new conception of the dynamic state of fat in the tissues,

largely through the brilliant work of the late Dr. Schoenheimer and his colleagues. As a result of the investigations of Hevesy, Chaikoff, Stetten and others, we have secured a great deal of new information on the formation and mobilization of the lipids. We now have a number of powerful agents which stimulate the mobilization of fat from one part of the body to another. Three of these — insulin, the lipotropic factors, and the pituitary liver fat increasing material — were discovered or first clearly demonstrated in our laboratories, and I shall describe briefly the effect of each of these on fat mobilization. The anti-fatty liver substance of Chaikoff and his collaborators, and Dragstedt's lipocaic, and their relationship to the problem will also be discussed.

The Absorption of Fat

It is high time that a vigorous new study utilizing the modern methods of fat estimation and identification should be made upon the process of absorption of fat from the intestines. Many aspects of this problem still remain obscure. It appears to be established that, except for small quantities which may be absorbed in a fine emulsion of unsplit fat, hydrolysis of the fat into its constituent fatty acid and glycerine is a necessary preliminary to absorption. Small amounts of paraffin oil, which is of course not digested, can be absorbed. Lanolin on the other hand, although well emulsified, is not absorbed. The importance of the bile salts in the passage of fatty acids across the intestinal membrane has been re-emphasized. Sinclair has found that during fat absorption a change occurs in the composition but not in the total quantity of phospholipids in the intestinal mucosa. During fat absorption the fatty acids of this specific phospholipid are those of the food fat. The belief that phosphorylation of the fatty acid occurs as a step in the synthesis of neutral fat in the intestinal mucosa, has been supported by Verzar, but serious doubt has been cast upon his evidence.

The Pathway of Absorption

One searches in vain for convincing new studies in which an attempt has been made to account for all of the fat which disappears from the intestines during fat absorption. We are forced to rely upon very old and rather dubious data which indicate that 60% or so of the fat can be detected in the lymph channels, i.e., in the thoracic duct. Many of us have cannulated the thoracic duct and watched fat absorption but no modern attempt has been made to place this observation upon a quantitative basis. An anatomical and biochemical, i.e., a physiological study, would be well worth while, even if no new channels were detected. Fraser believed that there is appreciable absorption directly into the blood stream, but this very stimulating work awaits confirmation and extension.

During fat absorption the central lacteals show rhythmic contractions which evidently serve to force the chyle in them into the lymphatic tributary to the thoracic duct. Under dark ground illumination, plasma fat can be observed as minute particles. Fat is, of

course, not only transported as chylomicrons but phospholipids and cholesterol esters are believed to act as vehicles. The lipoproteins may also play a role.

When one examines these matters closely, it will be found that the rise in phospholipids during fat absorption is small and irregular. The changes in cholesterol are even more indefinite and may be due solely to cholesterol which is delivered into the intestine when fat is being absorbed. While it is possible that the change in cholesterol from the free to the bound form may be of some significance, there is really little or no direct evidence based on changes in amount of blood, for the participation of cholesterol in the early stages of fat metabolism. But the participation of substances in the mobilization of fat must not be judged by variations in amount unless considered in relation to their rate of regeneration. Ten units of phospholipid may carry twenty new fatty acids on every trip or may carry the same fatty acids forth and back. The amount of phospholipid would remain the same in both cases. A beginning has been made in an investigation of this new possibility. Plasma phospholipid is apparently formed largely in the liver, since labelled phosphorus which readily finds its way into the plasma phospholipid under normal conditions, does not do so after hepatectomy. Certain dietary factors increase the rate of regeneration of the phospholipids of plasma.

Dietary fatty acids labelled in various ways have been detected in hepatic tissue after fat absorption. The older results in which various methods of labelling were used, and which demonstrated the deposition in the depot fat of dietary fatty acids, have been abundantly confirmed by the use of more modern and better techniques of identification. We have, however, no quantitative data to indicate whether all of the fat which is deposited in the tissues must pass through the liver before deposition in the fat depots. If some action of the liver is necessary it would seem to have been better to arrange for the absorption of fat into the blood, or to deliver the lymph containing the fat first to the liver rather than into the subclavian veins. Perhaps, however, a more gradual presentation of dietary fat to the liver is desirable.

The Dynamic State of Fat in the Tissues

As stated above, recovery from the depot fat of a particular dietary fatty acid has been repeatedly demonstrated. This deposition is, however, limited to the higher fatty acids — above C¹². Those of lower molecular weight are apparently called upon first for the provision of energy, or they may be built up into longer chains and stored. Thus the low molecular weight fatty acids may affect the composition of the body fat. Schoenheimer and Rittenberg has shown that a portion of stearic acid may be desaturated to oleic acid and another degraded to palmitic acid. Unsaturated bonds may be hydrogenated and a long chain fatty acid may be converted to a shorter or longer molecule. The inter-conversion of the fatty acids within the body is thus well-established. Desaturation was demonstrated by means of the isotope technique, but the more

highly unsaturated essential fatty acids were not formed. The animal body is capable of not only producing one type of fatty acid from others, but does so even if the fatty acid formed is abundantly supplied in the diet. While these steady interconversions are going on, fat formation takes place continuously and rapidly in normal animals whether fat is supplied in the diet or not, i.e., it comes from carbohydrate + protein.

This beautiful work, due largely to Dr. Schoenheimer and Dr. Rittenberg, shows that the lipids of the fat deposits are constantly subject to a great variety of chemical changes. The normal animal's body fat, despite qualitative and quantitative constancy, is in a state of rapid flux. It is obvious that this could not have been detected without the development of the use of isotopes.

I may state here that my colleagues and I, with a great deal of help from Dr. Schoenheimer, investigated the rate of regeneration of depot fats using deuterium as a label, and we did not find as rapid a rate of regeneration as Schoenheimer's experiments had established under other and more normal dietary conditions. We were using a more highly purified diet and supplied only one of the B vitamins — thiamine. Under these conditions the rate of turnover of depot lipids was apparently less than when the more complete diet had been used. Stetten and Grail have confirmed Schoenheimer's results and find the half life of deuterium in depot fat 5-6 days, and in liver fat 2.6 to 2.8 days. It may be that our incomplete diet interfered with the normal state of affairs, but these findings have already stimulated the further analysis of this situation.

Starvation

And now let us consider certain specific conditions and discuss how they affect fat transport — first, starvation. The gross changes in the fat depots during starvation are, of course, obvious. There have been numerous reports of a rise in the plasma lipids, but results vary from species to species. In some organisms it is accompanied by ketosis while in others very little rise in ketonemia can be demonstrated. In 1944, for example, Kartin, Man, Winkler and Peters, studied the changes in plasma and serum lipids in fasting normal man. There was a slight rise in ketone bodies and serum cholesterol and in lipid phosphorus, but there was no definite change in the neutral fat.

In some species the accumulation of fat in the liver is observed during starvation. In most laboratory animals, however, this is never very marked and in many of them it is difficult to demonstrate a definite increase. Under conditions when the rise in liver fat does occur during starvation, it has been demonstrated by the older methods of labelling, that a large part of the fat comes from the depots. More recently, using deuterium, workers in our laboratory have shown that the principal, if not the only source of fat which accumulates in the liver during fasting is transferred from the body depots. Starvation is perhaps the simplest condition with which we have to deal. The activities of

the various organs concerned with fat metabolism are presumably not impaired, and the complicating effect of diet on the picture has been eliminated.

Poisoning by Various Toxic Agents

Under these conditions, as for example carbon tetrachloride poisoning, the animals or patients are fasting or take very little to eat. In addition to this factor of starvation, there are definite pathological changes in the liver. Using the deuterium technique, my colleagues and I were able to show that the fatty acids which accumulated in the liver as a result of carbon tetrachloride poisoning came from the fat depots.

The Anterior Pituitary Liver Fat Increasing Substance

A considerable body of data has been obtained in our laboratories demonstrating the very definite increase in liver fat produced by fractions prepared from the anterior lobe of the pituitary. Using the deuterium technique, it is possible to show that here again most if not all of the fat accumulating in the liver, is derived from the depots. Stetten and Salcedo, using deuterium in a somewhat different way, have obtained identical results. The anterior pituitary material is used as a general rule in fasting mice or rats, so that the pituitary effect is really an augmentation of that seen in starvation. The effect of the pituitary extract is greatly diminished when the animals are fed.

Fat Mobilization of Diabetes

The gross changes in fat depots in diabetes are as obvious as in starvation and there is, of course, a tremendous loss of the fat reserves. There is a rise of phospholipids and cholesterol in plasma, and the liver may become very fatty. One has seen, for example, a liver containing 25% fat in a diabetic dog a week after pancreatectomy. The exact values depend upon the rate of onset of the diabetes, upon the diet, and perhaps other factors. The source of the blood and liver fat in diabetes has not, to my knowledge, been explored utilizing the newer technique. However, it would seem certain that it comes from the depot fat as in starvation or after injection of the anterior pituitary material. Stetten and Boxer have recently shown that approximately ten times as much carbohydrate is used to form fatty acids in the normal animal as to form glycogen. In the diabetic organism (rats made diabetic by alloxan) these authors have shown that the process of synthesis of fatty acids from carbohydrate sinks, under certain conditions, to only 5% of the normal rate. This fact, considered with the rapid loss of depot fat in diabetes, would appear to provide sufficient indirect evidence to justify the conclusion that the depots are the source of liver fat in the diabetic organism which is not receiving insulin.

The first demonstration of the action of insulin in preventing the fatty liver of diabetic animals was obtained by our group in Toronto in 1922. The fall of blood fat when insulin was given was also shown for the first time in the same experiments. No estimation was made in the depancreatized dog of the rise in

depot fat, but we, of course, know that this does occur in diabetics when insulin treatment is continued.

These changes in fat deposition occur with great rapidity when insulin is removed from the body or when it is administered to the diabetic organism. It may also be inferred from the work which Drury in California has carried out, and from the results of Stetten and his collaborators, that one of the actions of insulin in the normal animal is the promotion of fat formation from carbohydrate.

The Lipotropic Factors

Many of you are familiar with the work on depancreatized dogs which led to the identification of new dietary factors, for which I selected the name "lipotropic." Choline, Betaine, methionine and inositol may be considered as the physiological lipotropic agents. I will not discuss here the brilliant work of Tucker and Eckstein, du Vigneaud, Griffiths, and others, which has added so much to this story. Since betaine and methionine are precursors of choline in exerting their lipotropic action, we may consider first how mobilization of fat is affected by choline itself.

Welch showed that arsenocholine, i.e., the choline molecule with arsenic replacing the nitrogen, can be detected in the phospholipids of liver after it has been added to the diet. Stetten, using N^{15} , obtained similar results. He showed that the incorporation of a labelled choline occurred most rapidly in the liver. The results of Chaikoff, using radio-active phosphorus, indicate a more rapid turnover of the phospholipids when choline is administered. From these and from other results which I need not detail here, it is reasonable to conclude with Stetten that the action of the lipotropic factors, i.e., choline, betaine and methionine, is to increase the rate at which fat is transferred from the liver to the depots. The action of inositol, which supplements that of choline under certain conditions, has not been elucidated, but it may be related to an increased turnover of inositol containing phospholipids in liver, as McHenry has suggested. These lipids, however, have not as yet been identified in liver tissue.

The source of liver fat when rations low in choline and high in carbohydrates were fed, was shown (using the deuterium technique) not to be the fat depots, but was probably the carbohydrate of the diet.

When a diet low in the lipotropic factors is given to a depancreatized dog deprived of insulin, extremely fatty livers may be obtained. The resultant interference with hepatic function inhibits gluconeogenesis and only a mild glucosuria may be present.

Other Dietary Factors and Liver Fat

When thiamine, cystine, or biotin are added to diets deficient in these factors, or if certain liver extracts are fed to animals after they have been maintained on an incomplete diet, an accumulation of fat may be observed in the liver. This is due, in part at least, to an accelerated intake of carbohydrate or protein from which fat is formed in amounts which exceed for a time the capacity of the liver to deal with it.

The Anti-Fatty Liver Component of Pancreas Described by Chaikoff and his Collaborators

As some of you know, there has been a difference of opinion between Chaikoff and his group and Dragstedt and his collaborators, regarding the identity of the anti-fatty liver substance in pancreas which is not one of the lipotropic agents. Chaikoff, Entenman and Montgomery have shown that a fraction can be prepared from pancreas which is very low in choline and presumably in the other established lipotropic agents. This material still prevents fatty infiltration of the liver in depancreatized dogs, and recently these workers have suggested that this material is enzymatic in nature. I have entertained a similar idea regarding this fraction for several years, and in the autumn of 1944 the late Dr. A. H. Palmer began working in my laboratory on the pancreas fraction prepared by the Chaikoff method. Dr. Palmer was not in good health, but before his untimely death in April, 1945, he was able to isolate from the extract containing the anti-fatty liver fraction of pancreas, trypsinogen and chymotrypsin in crystalline form. He believed that still another proteolytic enzyme was present. These results of Palmer's lend direct support to the view that the anti-fatty liver fraction of pancreas used by Chaikoff et al may owe its activity to well-known proteolytic enzymes. This fraction would, therefore, be effective only in depancreatized dogs which have lost, in part, the ability to liberate the choline precursor, methionine, from protein. It is not, of course, established that this is the complete explanation of Chaikoff's findings.

Lipocaic

The pancreas preparation called lipocaic by Dragstedt, contains a moderate amount of protein which would provide methionine, a precursor of choline. There may also be a little choline, and perhaps a small amount of inositol. Chaikoff and his group have found lipocaic a poor source of their anti-fatty liver fraction which is effective in depancreatized dogs. Some years ago Dr. Ridout and I were unable to find evidence in rats that lipocaic contained a lipotropic agent other than choline and protein. These results were challenged by Dr. McHenry, who felt that we should have used the "biotin fatty liver" in our tests. Since our recent results show that the so-called "biotin fatty liver" reacts in essentially the same way as the type we previously used, our findings are, therefore, still interesting. We would be quite prepared to believe that lipocaic contains sufficient inositol to augment, somewhat, the action of the choline and methionine which is present. This augmentation is difficult to detect under some conditions. In my opinion, it still remains to be established that lipocaic contains any factors which affect the liver fat of the normal animal, with the exception of those lipotropic agents which have already been described. In depancreatized dogs it may, of course, exert some additional effect by virtue of its content of anti-fatty liver fraction of Chaikoff and his collaborators.

Potential Applications

We may consider very briefly how the various agents which mobilize fat in the body may be utilized. Insulin, of course, is specific in pancreatic diabetes and rapidly corrects the abnormalities in fat metabolism incident to this condition. The fatty liver of the diabetic child is probably due in all but the most exceptional cases to inadequate insulin therapy, rather than to lack of lipotropic factors in the diet. Insulin is not effective in producing more than a small change of fat when administered to a normal animal, but one can, of course, increase the appetite with insulin and deposit larger amounts of fat in the depots as a result of the ingestion of larger amounts of food.

The physiological significance of the substance in the anterior lobe of the pituitary which mobilizes depot fat to the liver so efficiently, is not established. Much more will have to be known about its significance in physiology and much more potent and pure preparations will have to be secured before any useful clinical investigations can be carried out.

The lipotropic agents are very effective in promoting transport of fat from the liver under conditions when the accumulation of fat in the liver is due only to a deficiency of these factors in the diet. We were once able to demonstrate some effect of the lipotropic agents in depancreatized dogs which had received no insulin. The effect was not as dramatic as an injection of insulin would have been, but the liver fat was definitely lower when large doses of choline were supplied. Choline or its precursors have relatively little effect in preventing fat deposition due to toxic agents although under certain conditions this action may be demonstrated. If, however, choline or its precursors are not supplied in adequate amounts in the diet, the accumulation of fat due to interference with liver function by toxic agents, will not disappear. (Methionine may exert protective effects against hepatic poisons due to an action other than that on fat metabolism.)

If the anti-fatty liver fractions of the pancreas, as Chaikoff has labelled the agent or agents which are effective in depancreatized but not in normal animals,

should prove to be the proteolytic enzymes of pancreas, a question asked many years ago by Professor Macleod and his collaborators, will be answered, in part at least, in the affirmative. The question was: when we feed pancreas and prevent the development of fatty livers in insulin-treated depancreatized dogs, is the action due to the pancreatic enzymes? From the therapeutic standpoint the effect of an enzymatic anti-fatty liver fraction would be confined to organisms which had lost a part of their ability to digest protein.

My friend Dr. Lester Dragstedt would probably agree with me when I suggest that a useful purpose would be served if several groups of investigators studied the same active preparation of lipocaic, to determine whether or not the recent additions to our knowledge of the lipotropic agents makes it unnecessary to postulate the presence of some still unidentified factor in pancreas which affects fat metabolism. Until this point is settled experimental or clinical results with lipocaic can certainly not be used as evidence for a second internal secretion of the pancreas, or for the existence of an unidentified dietary factor in pancreas.

The investigation of fat formation and transport in the body has recently become one of the very active aspects of physiological research. A continuation of this activity will enable us to write a much more complete account of the process in the not distant future; but you will observe that at present we have no knowledge of the mechanism by which the liver or the fat depots receive their signals when the agents which produce fat mobilization are administered.

Chairman Tolstoi: Are there any comments on Dr. Best's paper?

Before we adjourn, I would like to express the appreciation of the New York Diabetes Association, and I want to voice my thanks to both Dr. Best and Dr. Haist for coming here and giving us a very pleasant evening. I am sure most of us, all of us in fact, have been greatly stimulated by their thought-provoking papers, and in addition to that, our knowledge has been greatly enriched by what we heard this evening.

Thank you very much!

..Whereupon at 10:20 p.m. the meeting was adjourned..

Evaluation of Blood Sugar Tests: Significance of the Non-Glucose Reducing Substances and the Arterio-Venous Blood Sugar Difference

By

HERMAN O. MOSENTHAL, M.D.

and

EILEEN BARRY, B.S.

NEW YORK CITY, N. Y.

THE CORRECTNESS of the diagnosis and the efficiency of the treatment of diabetes mellitus largely depend upon the validity of blood sugar estimations, yet it is freely acknowledged that the accuracy of the tests for blood sugar is not firmly established. Two phases of this problem are considered in this report: the significance of the non-glucose reducing substances, and the interpretation of the arterio-venous blood sugar difference.

Laboratory Technique and Methods

The most widely used method for the determination of blood sugar is the Folin-Wu procedure. It is known that the sugar values reported by this test include a considerable quantity of so-called non-glucose reducing substances that are not glucose. The Folin-Wu method was used throughout this investigation as well as a determination of "true blood sugar."

For the determination of "true glucose" a special micromethod was devised. The problem was to obtain "a procedure simple enough so that a number of determinations could be carried out promptly, and yet sufficiently precise for investigations where relatively small differences in blood glucose values were anticipated and where samples of only 0.1 cc. of blood might be available for analysis." The method of Lauber and Mattice (1) was the result. This micromethod yields checks both for fermentable sugar and with the accepted procedures of determining "true blood sugar." All the determinations were carried out in duplicate. Without such a check it is curious how even the most skilled and conscientious technicians may slip into inaccuracies.

The finger-tip blood, the capillary blood, was obtained to determine the arterial blood sugar values. All workers conclude that the capillary, finger-tip, blood sugar levels are identical with those of blood derived directly from the arteries (2).

All venous blood specimens were obtained without the aid of a tourniquet because of the errors which its use brings about (3).

Results and Discussion — Non-glucose Reducing Substances

There are two types of blood sugar determinations in general use. One estimates the fermentable sugar,

presumably glucose; the other includes certain other reducing substances. The results of the first methods are often designated as "true glucose" while in the latter they are described as blood sugar, implying that the non-glucose reducing materials are included in the figures for glucose. The blood sugar method of choice is usually the Folin-Wu procedure which includes the non-glucose, non-fermentable reducing materials as sugar. The difference between the Folin-Wu results and the values obtained for true blood sugar yields the figure for non-glucose reducing substances.

It has been generally believed that the non-fermentable moiety produces an error of 10 to 30 mg. per 100 cc. of blood (4). Not only has this inaccuracy been regarded as "slight," but also as "fairly constant." In the first 200 blood sugar determinations carried out in this investigation (Table I) we found the total

TABLE I

Non-Glucose Reducing Substances in 200 consecutive Blood Sugar Determinations in Normals and in Diabetics, in the fasting state and after eating.

Non-Glucose Reducing Substances Venous Blood Mg. per 100 cc.	Number of Cases	Per cent	
0 - 10	40	20	62% within accepted normal limits.
11 - 20	47	23.5	
21 - 30	37	18.5	
31 - 40	41	20.5	38% above accepted normal limits.
41 - 50	15	7.5	
51 - 60	13	6.5	
61 - 70	3	1.5	
71 - 80	4	2.0	
Totals	200	100.0	

In 38 per cent of the determinations the amount of non-glucose Reducing Substances exceeded the accepted upper normal limit of 30 mg. per 100 cc.

non-glucose reducing substances to vary from 1 to 78 mg. per 100 cc. and that 38 per cent were above the accepted upper normal limit of 30 mg. per 100 cc. The difference in our results from those in the literature we believe is largely due to the great number of determinations carried out in contrast to the comparatively few used as a basis for previous statistics.

The non-glucose reducing substances have been considered as made up of glutathione, cysteine, fructose, ergothione, creatinine and undetermined materials. All attempts with the present data to correlate them with diet, insulin, etc., yielded no clues as to how to interpret the non-glucose reducing substances. Since they are composed of a large number of materials with various origins and functions, this would be the ex-

*Aided by a grant from the New York Diabetes Association, Inc. Read before the Research and Journal Club of the New York Post Graduate Medical School and Hospital, January 15, 1946. Submitted February 14, 1946.

pected finding. One of these studies is given in Chart 1. The non-glucose reducing substances were determined in the course of 25 sugar tolerance tests; the marked fluctuations without any definite pattern are evident.

The extent to which the non-glucose reducing substances can cloud the interpretation of sugar tolerance tests may be gathered from the following summary from 25 consecutive tests (see Chart 1):

In 9 cases (36 per cent) the non-glucose reducing substances were 30 mg. per 100 cc. or less in all the venous blood sugar determinations, that is within the accepted normal limits.

In 4 instances (16 per cent) the non-glucose reducing substances exceeded 30 mg. per 100 cc. in all the venous blood sugar determinations, thus topping the accepted normal limits throughout the sugar tolerance test.

In 16 instances (64 per cent) the non-glucose reducing substances exceeded 30 mg. per 100 cc. in at

least one of the venous blood sugar determinations.

When the non-glucose reducing substances are high they may lead to an erroneous interpretation of sugar tolerance tests (Table II) making it clear that true

TABLE II

High Values for Non-Glucose Reducing Substances in a Sugar Tolerance Test

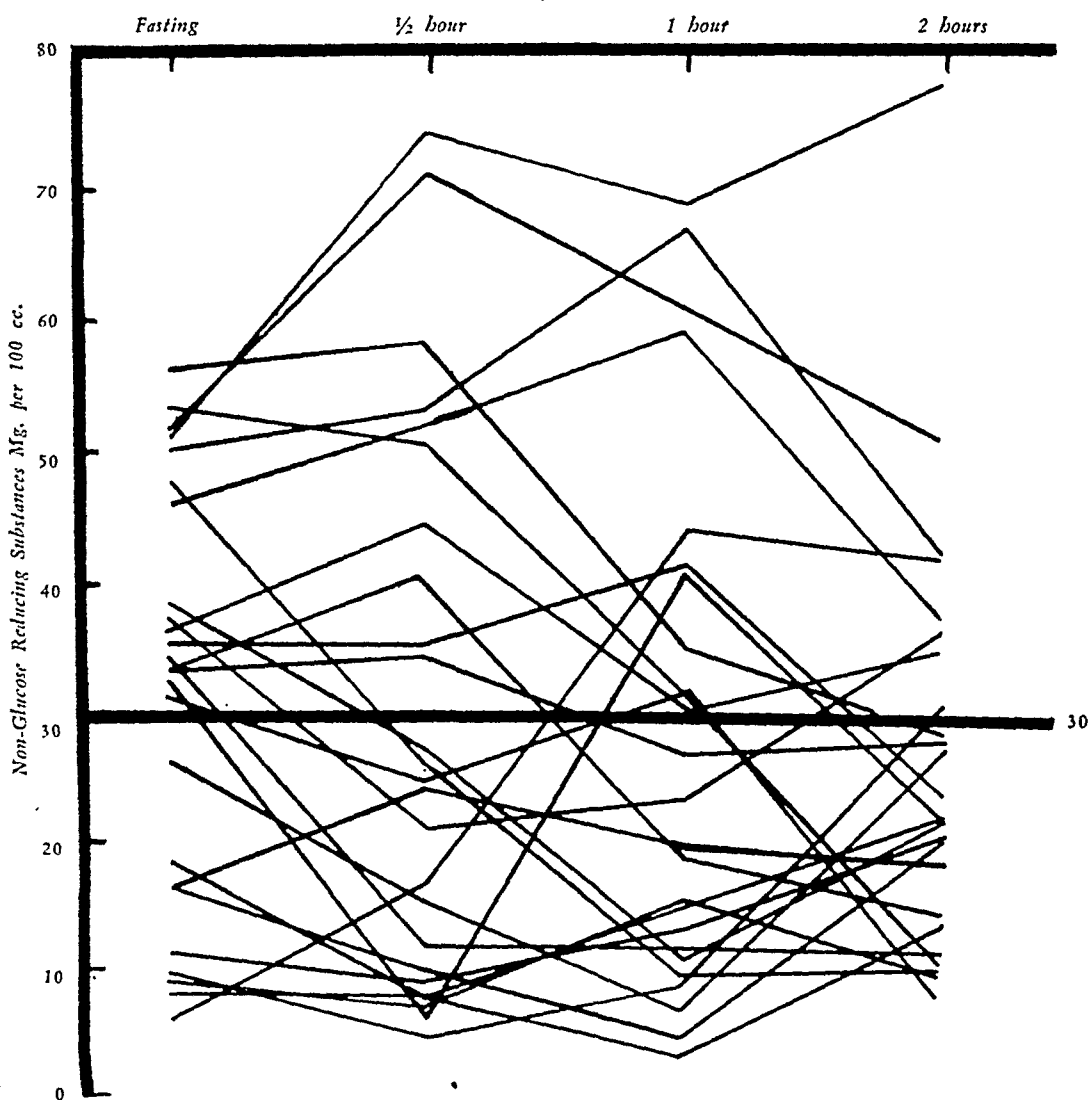
Timing	Venous Blood Sugar Mg. per 100 cc. True Blood Sugar	Venous Blood Sugar Mg. per 100 cc. Folin-Wu Method	Non-Glucose Reducing Substances Mg. per 100 cc.
Fasting	87	138	51
100 Gms. Glucose by mouth			
½ hour later	102	176	74
1 hour later	109	178	69
2 hours later	90	168	78

According to the true venous blood sugar this is a normal curve, while the Folin-Wu method indicates a diminished sugar tolerance. This is an example of the hazard of an erroneous interpretation of blood sugars when the analyses include non-fermentable substances, whereas the correct diagnosis is revealed by the true blood sugar determinations.

Male (S. B. G.) age 44. Glycosuria found on Life Insurance examination 7-8 years ago; no glycosuria since that time.

CHART I

*Non-Glucose Reducing Substances in 25 Sugar Tolerance Tests.
After 100 Gms. Glucose*



The marked fluctuations, without any definite pattern, are evident. Many determinations are above the accepted upper value of 30 mg. per 100 cc.

blood sugar methods will furnish a more satisfactory guide for judging glucose tolerance than will the Folin-Wu or other procedures that include non-glucose reducing substances. Since the variation of the non-glucose reducing substances is unpredictable, and their amount may be so great as to nullify the meaning of blood sugar values, it becomes evident that true blood sugar estimations are preferable in all clinical and experimental observations.

Results — Arterio-Venous Blood Sugar Difference

Heretofore the choice of either arterial or venous blood by the clinician has been considered of minor importance and not much attention has been paid to this subject. The same criteria in judging the significance of the blood sugar have been applied whether arterial or venous blood samples were analyzed, yet it is known that the arterial blood sugar is usually higher than the venous. In the first 200 consecutive determinations carried out mostly on diabetics, though some normals were included, under widely varying dietary conditions, it was found that the arterio-venous blood sugar values showed great fluctuations, the highest being 102 mg. per 100 cc. and the lowest minus 26 mg. (Table III). The amount of arterio-venous

TABLE III

Arterio-Venous true blood sugar differences in 200 consecutive determinations.

Arterio-Venous Blood Sugar Differences Mg. per 100 cc.	Number	Per cent
-21 to -30	2	1
-11 to -20	2	1
-1 to -10	14	7
0 to 10	61	30.5
11 to 20	52	26
21 to 30	24	12
31 to 40	27	13.5
41 to 50	5	2.5
51 to 60	5	2.5
61 to 70	5	2.5
71 to 80	1	.5
81 to 90	1	.5
91 to 100	0	0
101 to 110	1	.5
Totals	200	100.0

In only 9% of the determinations was the venous blood sugar higher than the arterial. In 35.5% the arterio-venous difference exceeded 20 mg. per 100 cc. of blood, which is often a significant variation in evaluating blood sugars.

blood sugar difference exceeded 20 mg. per 100 cc. in 35.5 per cent of our first 200 determinations (Table III). This degree of variation is of distinct significance in the interpretation of blood sugars either for the treatment of diabetes or for the evaluation of sugar tolerance tests. The highest figure obtained for the arterio-venous blood sugar difference was 102 mg. While this is an isolated instance, yet one such freakish metabolic episode may deprive a man of life insurance and may inflict a great burden of unnecessary medical attention upon him.

In only 9 per cent of the determinations was the venous blood sugar higher than the arterial (the greatest difference being 26 mg.). This is worth bearing in mind because it has been stated time and again

that in diabetes the venous blood sugar exceeds the arterial (5). Since the majority of the cases studied were diabetics it is obvious that in our series this is the exception rather than the rule even though diabetics are more prone to have a reversed arterio-venous difference than are normals (Table V).

For a number of years we have made extensive efforts to establish a sugar tolerance test by one simultaneous estimation of the capillary (arterial) and venous blood sugar, in the hope that the arterio-venous difference might distinguish between normals and diabetics, but this has proved to be a will-o'-the-wisp in spite of considerable study devoted to it. One of the reasons for the failure of this effort is the variability and unpredictability of the arterio-venous blood sugar difference. This is shown in Table IV which details

TABLE IV

Arterio-venous blood sugar differences in ambulant diabetics, about two hours after breakfast, when three or more determinations are carried out on the same patient.

Case	Date	True Blood Sugar Mg. per 100 cc.		Arterio-Venous Blood Sugar Difference
		Arterial	Venous	
J. M., Male Age 44	Dec. 1	475	438	37
	15	165	155	10
	29	176	145	31
	Jan. 12	415	390	25
	26	133	122	11
	Feb. 2	276	253	23
W. G., Male Age 50	16	276	272	4
	Jan. 3	296	298	-2
	28	276	280	-4
	Apr. 5	416	440	-24
	12	374	400	-26
	20	264	262	2
H. R., Male Age 32	May 3	269	253	16
	10	406	405	1
	Dec. 15	334	352	-18
	May 24	223	216	7
I. G., Male Age 49	Jul. 19	107	92	15
	Apr. 14	170	166	4
	May 8	287	280	7
	23	192	178	14

The variability and unpredictability of the arterio-venous blood sugar difference is evident.

a series of determinations in four diabetics at intervals under the same conditions.

In fasting normals and in fasting diabetics not receiving insulin, the arterio-venous difference varied from 1 to 17 in 11 normals, and from minus 15 to 30 in 27 diabetics (Table V). Curiously enough the average arterio-venous blood sugar difference for each group was 9. While the fasting arterio-venous blood sugar difference in fasting normals was prone to be low and approach the zero point, this was not a certainty. The reversed arterio-venous blood sugar difference that has been claimed as characteristic of diabetes (5) was found in only a small minority and cannot be regarded as an adequate diagnostic measure for the recognition of diabetes.

Two hours after breakfast in normals, in diabetics not receiving insulin and in those under treatment with insulin (Tables VI and VII) the arterio-venous blood sugar difference showed surprisingly slight increases as compared with that obtained in the fasting state (Table V). While the arterio-venous blood sugar difference tends to be higher in normals after breakfast

TABLE V

True arterial and venous blood sugars and arterio-venous blood sugar differences in fasting normals and fasting diabetics not receiving insulin.

Normals Fasting			Diabetics Fasting (not receiving insulin)		
True Blood Sugar Mg. per 100 cc.			True Blood Sugar Mg. per 100 cc.		
Art.	Ven.	A-V diff.	Art.	Ven.	A-V diff.
88	87	1	369	384	-15
95	91	4	120	122	-2
121	116	5	352	353	-1
106	101	5	177	178	-1
105	98	7	122	122	0
97	90	7	223	223	0
79	71	8	264	263	1
96	84	12	132	128	4
85	73	12	101	97	4
97	84	13	170	166	4
115	98	17	329	324	5
			206	200	6
			112	106	6
			287	280	7
			170	163	7
			230	222	8
			261	252	9
			207	195	12
			221	208	13
			118	105	13
			443	428	15
			229	211	18
			165	147	18
			120	102	18
			128	109	19
			143	117	26
			155	125	30

Summary:

	Normals	Diabetics
Number of cases	11	27
Art. B. S. average	99	206
Ven. B. S. average	90	197
A-v diff. average	9	9

While the fasting arterio-venous blood sugar difference in fasting normals is prone to be low and approach the zero point as noted in the literature, this is not always found to be true. The reversed arterio-venous blood sugar difference, that has been claimed as characteristic of diabetes, is found in only a small minority and can not be regarded as an adequate diagnostic measure for recognition of diabetes.

TABLE VI

True arterial and venous blood sugars and arterio-venous blood sugar differences in normals and diabetics, not receiving insulin, about 2 hours after breakfast.

Normals 2 hr. after Bkfst.			Diabetics 2 hr. after Bkfst. (not receiving insulin)		
True Blood Sugar Mg. per 100 cc.			True Blood Sugar Mg. per 100 cc.		
Art.	Ven.	A-V diff.	Art.	Ven.	A-V diff.
155	155	0	334	352	-18
88	85	3	133	131	2
108	104	4	221	218	3
121	117	4	300	296	4
98	89	9	199	193	6
78	69	9	95	88	7
110	101	9	276	268	8
91	81	10	150	142	8
100	88	12	105	97	8
82	70	12	184	175	9
109	94	15	286	276	10
133	112	21	115	104	11
184	148	36	146	134	12
105	67	38	252	238	14
175	136	39	230	216	14
			192	178	14
			227	211	16
			134	113	21

Summary:

	Normals	Diabetics
Number of cases	15	20
Art. B. S. average	115	214
Ven. B. S. average	101	204
A-V diff. average	14	10

While the arterio-venous blood sugar difference tends to be higher in normals after breakfast than on fasting (see TABLE V), yet the difference exceeds that obtained in the fasting individuals in only 3 of the 15 cases. In the diabetics the arterio-venous blood sugar difference after breakfast is practically identical with that obtained in fasting diabetics (see TABLE V).

TABLE VII

True arterial and venous blood sugars and arterio-venous blood sugar differences in diabetics, receiving insulin, about two hours after breakfast.

True Blood Sugar Mg. per 100 cc.				True Blood Sugar Mg. per 100 cc.			
Art.	Ven.	A-V diff.		Art.	Ven.	A-V diff.	
300	302	-2	R*	190	198	-8	P*
246	232	14	R	304	309	-5	P & R*
				423	428	-5	P & R
374	400	-26	G*	207	205	2	P
416	440	-24	G	197	193	4	P
302	307	-5	G	338	331	7	P
276	280	-4	G	165	155	10	P
276	279	-3	G	178	168	10	P
296	298	-2	G	202	190	12	P
406	405	1	G	285	272	13	P
264	262	2	G	263	250	13	P & R
77	73	4	G	205	191	14	P & R
223	216	7	G	349	331	18	P
62	49	13	G	415	397	18	P
269	253	16	G	351	328	23	P
123	105	18	G	239	216	23	P & R
115	97	18	G	276	253	23	P & R
235	201	34	G	201	178	23	P & R
475	440	35	G	126	102	24	P & R
475	438	37	G	340	316	24	P
311	271	40	G	257	229	28	P & R
				176	145	31	P
				324	290	34	P
				485	450	35	P & R
				262	223	39	P & R

In these cases, treated with insulin, as in the studies of diabetics not receiving insulin, there are a few cases showing a reversed arterio-venous blood sugar difference, while the majority approximate the values obtained in normals (see TABLE VI). The arterio-venous blood sugar difference is about the same whether the insulin used is globin, protamine or a mixture.

*R indicates that the case was being treated with regular (unmodified) insulin, G with globin insulin with zinc, P with protamine zinc insulin, P & R with a mixture of protamine zinc and regular insulin.

than on fasting, yet the difference exceeded that found in fasting individuals in only 4 of 15 cases. In the diabetics without insulin the arterio-venous blood sugar difference after breakfast is practically identical with that obtained in fasting diabetics. In the insulin treated diabetics the arterio-venous blood sugar difference two hours after breakfast is about the same whether the insulin used is globin, protamine or a mixture. The results in the diabetics with insulin and those without were very much alike.

For a more satisfactory orientation in regard to the effect of food on the arterio-venous blood sugar difference a series of observations was made on normals and on diabetics over a four-hour period following the mid-day meal (Table VIII). Here again no appreciable variation was evident coming on after the taking of food and there was no notable distinction in the arterio-venous blood sugar difference, produced by lunch, between normals and diabetics treated with insulin.

During sugar tolerance tests, after the ingestion of 100 grams of glucose, diabetics as well as non-diabetics showed a very marked rise in arterio-venous blood sugar difference (Table IX). This is in contrast to the results obtained after eating breakfast or lunch and shows that a very marked and rapid rise of the blood sugar will bring about a clear-cut increase of the divergence of the arterial and venous blood sugar values.

TABLE VIII

True arterial and venous blood sugars and arterio-venous blood sugar differences for four hours following lunch in four normals and twelve diabetics.

C A S E			TRUE BLOOD SUGAR MG. PER 100 cc.																	
			LUNCH Gms.			BEFORE LUNCH			A F T E R L U N C H											
									1 Hour			2 Hours			3 Hours			4 Hours		
Age	State	Insulin*	Pro	Fat	CH	Art	Ven	A-V	Art	Ven	A-V	Art	Ven	A-V	Art	Ven	A-V	Art	Ven	A-V
18	Normal	0	30	20	50	78	68	10	88	76	12	82	80	2	108	95	13	80	77	3
22	Normal	0	30	10	40	87	80	7	69	62	7	78	72	6	74	70	4	60	60	0
21	Normal	0	60	40	115	90	88	2	110	102	8	88	80	8	106	100	6	82	80	2
22	Normal	0	25	20	40	95	83	12	76	66	10	91	80	11	83	82	1	95	87	8
Average Normals						88	80	8	86	77	9	85	78	7	93	87	6	79	76	3
15	Diabetic	P30 R15	33	18	57	47	44	3	103	98	5	156	142	14	172	158	14	155	143	12
18	Diabetic	P59 R44	46	30	103	68	56	12	186	170	16	232	220	12	242	230	12	310	302	8
22	Diabetic	P78	48	33	98	82	78	4	152	146	6	198	192	6	142	132	10	186	178	8
14	Diabetic	P40 R80	40	40	80	90	85	5	140	132	8	132	126	6	172	160	12	220	210	10
15	Diabetic	P27 R30	34	24	81	97	90	7	122	108	14	134	126	8	160	158	2	176	170	6
14	Diabetic	P30 R60	31	32	94	221	210	11	240	228	12	252	239	13	230	225	5	247	235	12
16	Diabetic	P65 R15	34	31	85	250	230	20	204	200	4	268	260	8	282	276	6	200	186	14
12	Diabetic	G30	36	29	75	290	286	4	310	304	6	400	402	-2	504	499	5	374	370	4
15	Diabetic	P20	35	45	81	309	297	12	340	329	11	345	356	-11	292	284	8	382	370	12
13	Diabetic	P55	31	23	68	380	366	14	404	394	10	454	438	16	568	551	17	300	288	12
16	Diabetic	P54	48	39	164	463	460	3	582	576	6	452	441	11	538	530	8	382	368	14
14	Diabetic	P18 R42	40	18	73	666	666	0	460	450	10	502	488	14	500	490	10	470	460	10
Average Diabetics						247	239	8	270	261	9	294	286	8	300	291	9	284	273	11

The arterio-venous blood sugar difference is not materially changed by eating lunch, that is an average meal. (This is in contrast to the effect of taking 100 gms. of glucose, see TABLES IX and X. There is no notable distinction in the arterio-venous blood sugar difference, produced by lunch, between normals and diabetics treated with insulin.

*P indicates that the case was being treated with protamine zinc insulin, R with regular (unmodified) insulin, G with globin insulin with zinc.

TABLE IX

True arterial and venous blood sugars and arterio-venous blood sugar differences in diabetics and non-diabetics during sugar tolerance tests after 100 gms. of glucose.

True Blood Sugar Mg. per 100 cc.

Case	Before Glucose			After 100 Gms. Glucose								
	Fasting			30 min.			1 hour			2 hours		
	Arterial	Venous	A-V difference	Arterial	Venous	A-V difference	Arterial	Venous	A-V difference	Arterial	Venous	A-V difference
C.H.	87	78	9	217	178	39	212	154	58	117	62	55
G.S.	88	87	1	132	102	30	134	109	25	127	90	37
R.A.	97	84	13	132	97	35	134	109	25	120	85	35
G.G.	97	90	7	200	175	25	170	146	24	114	77	37
B.S.	101	97	4	227	178	49	281	216	65	128	79	49
R.L.	104	96	8	169	139	30	174	139	35	137	115	22
A.M.	105	99	6				190	165	25	157	123	34
M.S.	106	101	5	226	183	43	229	178	51	135	87	48
L.H.	112	106	6	150	142	8	160	141	19	208	191	17
S.M.	118	105	13	229	206	23	318	259	59	312	247	65
W.J.	120	122	-2	262	232	30	297	243	54	235	200	35
B.B.	121	116	5	207	169	38	166	137	29	133	98	35
F.C.	122	122	0	257	254	3				364	321	43
F.A.	125	112	13	258	220	38	304	262	42	188	158	30
C.J.	132	128	4	263	255	8	414	397	17	497	460	37
B.B.	128	109	19	200	189	11	275	206	69	225	144	81
R.T.	155	125	30	237	223	14	269	203	66	162	138	24
B.R.	170	163	7	392	290	102	250	176	74	212	151	61
K.R.	177	178	-1	287	282	5				486	484	2
C.N.	207	195	12	341	308	33	426	386	40	512	474	38
Ave.	124	116	8	231	201	30	245	202	43	229	189	40

The very marked rise in arterio-venous blood sugar difference after glucose ingestion is very evident. It far exceeds that occurring after food intake.

It is established that insulin accelerates the formation of muscle glycogen from blood glucose. Consequently it might be surmised that an insulin injection would augment the arterio-venous blood sugar difference. This was tried out (Table X) and it was found that at the second hour after insulin there was a definite rise in the arterio-venous blood sugar difference in spite of the fact that the blood sugar levels had dropped considerably. Such an increase in the arterio-venous blood sugar difference was not evident in one hour, three hours or four hours after the insulin injection but only at the second hour.

In order to compare the four-hour effect of insulin with that resulting from glucose administration, four individuals were subjected to a four-hour glucose tolerance test (Table X). For the first two hours the arterio-venous difference was much greater than after insulin, but then fell off so that it was distinctly below the control level by the fourth hour.

Discussion — Arterio-Venous Blood Sugar Difference

It is now established that the origin of glucose within the body is confined to two sources: absorption of food from the intestines, and, breakdown of glycogen by the liver. These are the factors that increase the sugar in the arterial blood. As the arterial blood passes through the capillaries of the various tissues some of the sugar is utilized and removed from the arterial blood. Consequently the venous blood sugar represents arterial blood sugar less the amount of sugar metabolized by the tissues, which can be expressed as the arterio-venous blood sugar difference.

TABLE X

True arterial and venous blood sugar determinations for 4 hours after the injection of insulin and after the administration of glucose.

Case	Before Insulin						After 20 Units unmodified Insulin											
	Fasting			1 hour			2 hours			3 hours			4 hours					
	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.
G.L.	146	128	18	91	74	17	82	60	22	74	66	8	80	76	4			
E.J.	229	211	18	184	167	17	149	142	7	122	117	5	132	120	12			
P.J.	264	263	1	232	233	-1	207	193	14	188	180	8	167	153	14			
W.B.	352	353	-1	341	349	-8	259	234	25	173	151	22	150	141	9			
P.D.	443	428	15	406	386	20	211	186	25	131	119	12	142	133	9			
Ave.	287	277	10	251	242	9	182	163	19	138	127	11	134	125	9			

	Before Glucose						After 100 gms. Glucose											
	Fasting			1 hour			2 hours			3 hours			4 hours					
	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.	Arterial	Venous	A-V diff.
J.W.	101	99	2	296	265	31	222	170	52	114	106	8	93	88	5			
R.L.	104	96	8	174	139	35	137	115	22	95	98	7	87	82	5			
A.M.	105	99	6	190	165	25	157	123	34	147	125	22	79	73	6			
F.A.	125	112	13	304	262	42	188	158	30	167	144	23	93	90	3			
Ave.	109	102	7	241	208	33	176	142	34	131	118	13	88	83	5			

The blood sugar curves follow the well established pattern of a 3 to 4 hour drop after insulin and of a sharp rise followed by a marked drop, below the fasting level, at the 4th hour, after glucose. The arterio-venous differences show a marked rise after glucose but only a slight rise after insulin.

The sole change which occurs during the passage of the blood from the arteries through the capillaries to the veins is effected by osmosis. The processes commonly associated with sugar metabolism, the breakdown of glucose by phosphorylation or oxidation, and the synthesis to glycogen, occur in the tissues after diffusion from the blood has taken place, but not in the blood stream. The obligatory first step in modifying the arterial blood sugar level and the development of an arterio-venous difference is therefore diffusion between the blood and the surrounding tissues which in the forearm are the skin and the muscles. The assertion has been made that the median basilic or the median cephalic vein at the bend of the elbow drain only the skin and not the muscles. According to the anatomical records, however, these veins, which are the usual site of venipuncture, also derive blood from the deeper tissues, presumably the muscles. In this discussion it has been assumed that the blood obtained at the bend of the elbow has passed through the capillaries serving both muscle and skin.

The absorption of glucose by the tissues from the blood appears to be a major influence in determining the blood sugar level. Trimble and Carey (6) showed that the amount of sugar in the skin and muscles was directly proportional to that in the blood, though lower in the tissues than in the blood. This difference may be accounted for by the breakdown of glucose or the formation of glycogen after the distribution of glucose to the tissues has taken place. Cori (7), on the other hand, found the glucose concentration in the tissues of the rat to be exactly equivalent to that in the blood. He calculated that 15 per cent of the body's free glucose existed in the blood. At a blood sugar level of 100 mg. per 100 cc., according to Cori's estimates,

there would be approximately 30 grams of sugar in the extra-vascular tissues of a human being. Peters and Van Slyke (4a) put the possible amount of sugar somewhat higher. They state that if it is assumed that glucose is evenly distributed throughout the water of the body the total amount of glucose in a 70 kilo man with a blood sugar of 100 mg. per 100 cc. can not exceed 50 grams as compared to 35 grams, (5 grams in the blood and 30 grams in the tissues) the figures derived from Cori's observations on the rat.

According to these calculations when the blood sugar rises from a fasting level of 100 up to 200 mg. per 100 cc., as it often does in sugar tolerance tests, there would be an increase of 5 grams of glucose in the blood and 30 to 45 grams in the other tissues. The point of this commentary is that the diffusion of glucose from the blood plays a big role in the disposal of glucose, especially after the ingestion of large amounts of sugar, as in sugar tolerance tests. The breakdown of glucose and the formation of glycogen by the tissues is probably accomplished by the tissues only after they have absorbed glucose so that the rate of glucose diffusion from the blood is a measure of all of the sugar metabolism that occurs in the tissues. The accomplishment of the process of glucose diffusion from the blood to the tissues obviously can be measured by the venous blood but not by the arterial blood sugar level.

The rate and direction of glucose diffusion are governed by many influences and are not the result of a unitarian cause. The velocity of blood flow, the intracapillary pressure, the widespread and ever changing opening and closing of the capillaries on many and various stimuli, are all involved. Also according to Krogh (8), the veins, in the skin at least, are associated with the exchange of substances between the blood and the

tissues. A rise in the arterial blood sugar, whether resulting from food intake or from hepatic glycogenolysis, causes absorption of sugar by the tissues at a rate proportional to the development of the hyperglycemia. The formation of glycogen and the breakdown of glucose depress the glucose level in the skin and muscle thus favoring further passage of glucose from the arterial blood. When the arterial blood sugar is sharply depressed after it has been markedly elevated as occurs in the third and fourth hours following the administration of glucose and happens frequently in diabetes, then the sugar in the tissues may exceed that in the arterial blood and a reversal in glucose diffusion may come about rendering the venous blood sugar higher than the arterial.

All these facts are mentioned to clarify two theses: first the arterio-venous blood sugar difference is within certain limitations a measure of sugar metabolized in the forearm, and second that many factors are concerned in the production of the arterio-venous blood sugar difference. It was shown in the section concerning results of the arterio-venous blood sugar observations that moderate stimuli from average meals and comparatively small doses of insulin have no appreciable effect on the rate of glucose utilization in the muscles and skin. This is true, of course, only in the clinical sense because the physician's opportunity for accuracy and finality in recording physiological occurrences is very limited. The variability of the arterio-venous blood sugar difference during the fasting state in diabetics as well as in normals is contrary to the current belief that it is more or less non-existent in normal persons and usually reversed in diabetes. However, when the multiplicity of influences which modify the arterio-venous blood sugar differences are taken into account it is not to be wondered at that uniformly fixed values do not exist. With dominant stimuli such as the ingestion of 100 grams of glucose the changes in the arterio-venous blood sugar become predictable as shown by a uniformly marked rise reaching its maximum one to two hours after the taking of glucose.

For the guidance of the treatment of diabetes and the carrying out of sugar tolerance tests, the venous blood sugar is preferable to the arterial because all the processes which contribute to the arterio-venous blood sugar difference are concerned with the better utilization of glucose and are therefore indicative of the degree of efficiency of the carbohydrate metabolism. There is one condition in which the arterial blood sugar is distinctly preferable to the venous. This is the determination of the renal threshold to glucose and ascertaining whether a renal glycosuria exists. It is the arterial blood which courses through the glomerular tuft and is the stimulus to filtration that takes place in that structure, while the venous blood is in no way concerned with the filtration of glucose in the production of glomerular urine. Yet nearly all clinicians and investigators have pinned their faith on the venous blood sugar levels for judging the point at which detectable amounts of sugar appear in the urine. The generally appreciated fact that urine voided in the

during the second hour of a sugar tolerance test exhibits a lower renal threshold to glucose than during the first hour, may be explained by the finding that during the second hour the arterio-venous blood sugar difference is very high, in the neighborhood of 40 mg. per 100 cc. (see Table IX) and that in reality the renal threshold may be unchanged if estimated according to the arterial blood sugar. It is evident that the renal threshold to glucose should be judged by true blood sugar levels obtained in arterial blood. Our present conceptions on this matter require extensive revision because hitherto the venous blood sugar, estimated by methods including non-glucose reducing substances, has been the measure for the calculation of the renal threshold to glucose.

Summary and Conclusions

Only the methods yielding "true blood sugar" values should be employed. Many procedures, such as the widely used Folin-Wu method, furnish results for glucose which include other substances than sugar. The so-called non-glucose reducing substances, which have no significance in sugar metabolism, exceeded the accepted upper limit of 30 mg. per 100 cc. in 38 per cent of 200 consecutive determinations and in four instances they were above 70 mg. In judging sugar tolerance tests it may be found that the true blood sugar values furnish proof of normal tolerance while the methods including the non-glucose reducing substances may erroneously indicate the existence of diabetes. It is recommended that only true blood sugar estimations be used in carrying out sugar tolerance tests and for the routine clinical observations on diabetics.

The arterio-venous blood sugar difference varies widely, from minus 26 to 102 in 200 consecutive tests. A minus, that is a reversed difference, is found more often in diabetics than in normals but it is by no means a constant occurrence in diabetes as some reports have claimed. In fasting normals and in fasting diabetics not receiving insulin while the arterio-venous difference was low it was not constantly so as stated in the literature. In fact the arterio-venous blood sugar difference was about the same whether the subject was fasting or had eaten, whether diabetes existed or not and whether the diabetic was or was not being treated with insulin. The arterio-venous blood sugar difference was prone to vary widely in the same individual on different days under like conditions of diet and insulin dosage. The injection of moderate doses (20 units) of insulin did not result in marked changes in the arterio-venous blood sugar difference.

On the other hand when stimuli were made sufficiently powerful a definite trend could be noted in the arterio-venous blood sugar difference. A sudden rise of the arterial blood sugar, as occurs after the administration of glucose, results in a marked divergence of the arterial and venous blood sugars, in one instance as high as 102 mg. per 100 cc. When the marked hyperglycemia is followed by a drop in the blood sugar it is natural that reverse diffusion, signaled by an excess of venous over arterial blood sugar, should

manifest itself. The minus blood sugar differences often found in diabetes can be explained on this basis. The eating of routine meals, in normals and in diabetics, has no demonstrable effect upon the arterio-venous blood sugar difference.

The arterial (capillary) blood sugar should be used to determine the level of the renal threshold to glucose

for the diagnosis of renal glycosuria. For the guidance of the treatment of diabetes and the carrying out of sugar tolerance tests, the venous blood sugar is preferable, because all the factors which contribute to increase the arterio-venous sugar difference and lower the venous blood sugar as compared to the arterial, are concerned with the better utilization of glucose.

REFERENCES

1. Lauber, F. U. and Mattice, M. R.: Microdetermination of blood glucose, *J. Lab. & Clin. Med.*, 29:113-116 (January) 1944.
2. a) Foster, G. L.: Studies on carbohydrate metabolism. 1. Some comparisons of blood sugar concentrations in venous blood and in finger blood, *J. Biol. Chem.*, 55:291-301, 1923.
b) Jonas, L.: A note on cutaneous venous blood sugar difference in normal males and females and in thyroid disease, *J. Clin. Investigation*, 12:139-141, January, 1933.
c) Langner, P. H., Jr., and Fies, H. L.: Blood sugar values of blood obtained simultaneously from radial artery, antecubital vein and finger, *Am. J. Clin. Path.*, 12:559-562, November, 1942.
3. Loughlin, W. C., Mosenthal, H. O., and Halpern, R.: Effect of tourniquets on venous blood sugar values, *J. Lab. & Clin. Med.*, 28:1165-1167 (June) 1943.
4. a) Peters, J. P. and Van Slyke, D. D.: Quantitative clinical chemistry, Volume I, Interpretations, The Williams & Wilkins Co., Baltimore, 1931.
b) Mattice, M. R.: Clinical procedures for clinical laboratories, Lea & Febiger, Philadelphia, 1936.
c) Sevringhaus, E. L.: The glucose tolerance test in Diagnosis of diabetes and hyperinsulinism, *Proceedings of the American Diabetes Association*, 4:119-139, 1944.
5. a) Holst, J. E.: Untersuchungen ueber leichte Glykosurien, *Acta. Med. Scand.*, 57:188-, 1922-1923.
b) Lawrence, R. D.: Effect of insulin on the sugar content of arterial and venous blood in diabetes, *Brit. M. J.*, 1:516-517, March 22, 1924.
c) Rabinowitch, I. M.: Simultaneous determinations of arterial and venous blood sugars in diabetic individuals, *Brit. J. Exp. Path.*, 8:76-84, February 1927.
d) Friedenson, M., Rosenbaum, M. K., Thalheimer, E. J. and Peters, J. P.: Cutaneous and venous blood sugar curves. 1. In normal individuals after insulin and in liver diseases. *J. Biol. Chem.*, 80:269-288, November, 1928.
6. Trimble, H. C. and Carey, B. W. Jr.: On true sugar content of skin and muscle in diabetic and non-diabetic persons. *J. Biol. Chem.*, 90:655-663, March 1931.
7. Cori, C. F.: Mammalian Carbohydrate metabolism. *Physiol. Rev.*, 11:143-275, April 1931.
8. Krogh, A.: The anatomy and physiology of capillaries. Yale University Press, New Haven. 1927.

DISCUSSION

By

EDGAR W. BECKWITH, M.D.

Associate Medical Director, Equitable Life Assurance Society, New York City

When Dr. Mosenthal invited me to discuss his paper, he suggested that I approach the subject from the standpoint of life insurance medicine, and therefore it should be distinctly understood that the opinions expressed in this discussion are neither those of a clinical specialist in diabetes nor those of an investigator in physiological chemistry. My basic premise therefore is, that in judging the conclusions reached in Dr. Mosenthal's paper, it must be recognized there are certain considerations which constitute common ground for both the clinician and the medical officer of an insurance company. On the other hand, there are considerations which are necessarily different, because they arise from different methods of approach to the problem of evaluating the significance of glycosuria.

In reviewing the first portion of the paper, with particular reference to the chemical method employed, it is my opinion that the standardized use of some micro method yielding only "true blood sugar" values, is highly desirable. In the laboratory of my own company, The Equitable Life Assurance Society, we have used since 1928 the Folin Micro method exclusively. It is believed that this method does not entirely eliminate the non-glucose reducing substances, but that, at any rate, the findings contain a much less margin of error than the results obtained by the Folin-Wu method.

The analysis presented of the difference in arterial and venous blood sugar values is indeed of great interest. It is to be regretted that so much confusion has entered the picture in establishing criteria of "normal" and "abnormal" findings, this confusion arising out of carelessness in reporting the source of the blood used and the chemical method employed. Even today one hears phy-

sicians, both in clinical and life insurance medicine, ascribe arbitrarily a difference of 20 mgs. to arterial and venous values in spite of repeatedly reported facts to the contrary. The fallacy of using such a figure is well illustrated by the charts shown.

It may be of interest to introduce a table showing a report on arterio-venous differences in blood sugar in normal individuals, using 50 grams of glucose, simultaneous puncture of finger and vein, and giving fasting, one-half hour and two hour blood observations by the Folin-Malmros method. This table appears in a paper prepared by Dr. Devces and Dr. Langner of the Provident Mutual Life Insurance Company and is recorded in the Proceedings of the Association of Life Insurance Medical Directors, Volume XXIX, 1942. Unfortunately, the number of the observations is not specifically stated, but the results strongly tend to confirm the findings of Dr. Mosenthal. Table:

Arterio-Venous Differences in Blood Sugar During the Two-Hour, One-Dose Tolerance Test

	Fasting	½ Hour	2 Hour
Average Difference	09	17.8	7.3
Maximum Difference	14	35	30
Minimum Difference	0	2	0

One is indeed impressed by Dr. Mosenthal's conclusion — based on the physiological chemical assumption that the arterial-venous difference represents the true criteria in the evaluation of sugar metabolism — that it would seem to be highly desirable, from a strictly scientific standpoint, that all observers adopt a "true blood value" method, using venous blood. On the other hand, he admits that there are a "multiplicity of influences" which modify the arterio-venous blood sugar differences; and it is also obvious, as he states, that the use of capillary blood is the only correct diagnostic procedure in cases of renal glycosuria.

Certainly, the adoption of any standardized procedure which gives presumably "true values" and therefore

tends to produce homogeneity of statistics is to be recommended.

At this juncture, it seems desirable to explore the situation from the standpoint of those of us who are engaged in the practice of life insurance medicine and to compare our point of view with that of the clinician. Basically, we are all doctors, and therefore scientifically inclined, even though, of necessity, our paths may sometimes diverge in our scientific pursuits. We should not be on different sides of a fence, but it is reasonable to examine the question objectively and to continue any different points of view from which we approach the problem of glycosuria.

The clinician, especially if he is a highly trained specialist, is usually contented with this situation. The patient comes to him (frequently referred by a general practitioner who feels that he has inadequate knowledge of a complicated problem) either because he has symptoms of diabetes, or because during a routine health or a life insurance examination sugar has been discovered in the urine. The clinician is called upon to answer three questions: "1. Has the patient diabetes?" 2. If so, how severe is the disease? 3. How successfully can it be controlled by diet, insulin, and other measures?" In seeking the answers to these questions the clinician has available to him certain data based on observations derived from his own experience or on reports made by other observers over a considerable number of years. The answer to the first question is not always easy because of the various definitions which have been proposed by different observers. In dealing with the second and third questions, it seems fair to state that, to a certain extent, a trial and error method must be followed in the care of almost every individual, and, with changing conditions, the treatment has to be altered on future occasions. The clinician is in the position of having as a patient an individual who often is alarmed by the possible seriousness of his condition, and who, therefore, will submit to any reasonable number of tests in order to determine the facts, and will also undergo treatment to maintain his health. Furthermore, if the clinician has the requisite knowledge and skill, and his treatment is successful, he usually has the opportunity to observe his patient, and to revise his opinion over the period of time during which the patient is under observation.

On the other hand, the medical officer of a life insurance company is in quite a different position. He is asked to evaluate a risk expressed in terms of a certain amount of money. In reaching his decision, he is able to obtain, in a rather limited way, certain data which assist him in classifying the risk according to the underwriting criteria in use in his company. He also has to his advantage the fact that these criteria are based on the so-called "experience" of the company. The "experience" of the company reflects the ultimate results derived from having insured many individuals with similar impairments over many preceding years. The scope of the investigation to ascertain the facts is limited, however, because, generally speaking, the applicant for life insurance believes himself to be in good health, and his attitude, in contradistinction to that of the patient, usually is, that he will not devote the time or effort to study thoroughly a possible impairment which he considers of no great importance.

This places a medical officer in a position where he often must make a decision on what a clinician might regard as meager evidence. His decision involves either acceptance of the risk at standard rates in presumably normal individuals, or acceptance of the risk in impaired individuals with an appropriate extra premium charge, or total rejection of the risk where the impairment is sufficiently marked to be unacceptable under the rules

of his company. The point which I wish to stress, however, is that once his decision has been made and his company has entered into a life time contract with the individual, he rarely has the opportunity to evaluate the validity of his original decision. The only circumstances under which he might ascertain anything as to the correctness of his judgment are three in number:

1. If the individual applies for additional insurance at a later date and therefore submits to a physical examination.
2. If the policy lapses for nonpayment of the premium and the insured applies for reinstatement of his contract and is again examined.
3. If the policy matures as a death claim and it comes to the attention of the medical officer, assuming that he is still alive and employed.

Another basic difference in the situation is that the clinician deals with an individual as a patient, whereas an insurance company, by the very nature of the theory of its nature, must perforce deal with the average result obtained from insuring large groups of people, and the company therefore obviously cannot in any way predict the outcome in any individual. It follows, therefore, that no system of selection can attain perfection. Any system will inevitably include an undesirable risk and exclude a desirable one; or in other words, an economic injustice may be done to the other policyholders of a medical company at the first instance and to the individual applicant in the second instance. However, again the law of averages operates, and a risk which one company will not insure, another company may, so that it is indeed rare to find an individual who fails to obtain insurance if it is at all possible under the broad rules observed by most companies.

At this juncture, I must admit — with reluctance — that the variation in insurance company practice in obtaining data and in evaluating the risk is probably quite comparable to the degree of variation of opinion among clinicians as to diagnosis and treatment. Generally speaking, the practice among insurance companies is to insure risks with glycosuria for comparatively small amounts based on evidence derived from urinary specimens alone. These specimens are usually about one and one-half to two hours postprandial (the meal containing a fair amount of carbohydrates) and a sufficient number of specimens are obtained to classify the risk from the standpoints of incidence and amounts of glucose in the urine. Admittedly this leads to fallacious conclusions in the rather uncommon true renal glycosurias.

In cases in which the company requires a blood sugar test, the practice varies rather widely. A few companies rely on fasting blood sugar alone; others require the ingestion of 50 to 100 grams of glucose, but are interested only in the fasting finding and in the single other finding at the end of either one and one-half, two, or two and one-half hours; others follow the more or less classical procedure of using 50 to 100 grams of glucose, and plotting a curve covering the findings (a) fasting, (b) one-half hour, (c) one hour, (d) two hours after ingestion. The insurance situation is further complicated by the fact that many companies, especially the smaller ones without adequate Home Office laboratory facilities, employ local laboratories and fail to specify the technique to be employed. Consequently, they often do not know whether capillary or venous blood was used or what chemical method was employed. All of this is regrettable, but I rather imagine that a somewhat similar clinical situation obtains throughout the country, with the exception of instances where the practitioner limits his practice exclusively to diabetes, and therefore carefully supervises his own laboratory.

I come now to the practice of my own company, The Equitable Life Assurance Society, initiated in 1925 by

Dr. F. G. Brathwaite. Prior to that time, insurance companies had insured relatively few glycosurics and those who were insured usually were accepted on the basis of a substantial extra premium. However, with the increasingly frequent usage of blood sugar determinations as a diagnostic aid, we embarked on the sea of adventure by insuring these individuals. During the first year or so, we accepted meal tests, which was obviously an unsound procedure as shown by Dr. Mosenthal's tables. However, this procedure was quite promptly abandoned in favor of glucose ingestion; and since that time we have used 75 grams of glucose, capillary blood, blood and urine observations made fasting, one-half hour, one hour, and two hours, *all specimens sent to our Home Office laboratory,* the blood being examined by the Folin Micro method. As to the mechanics of obtaining the material, we send the original examiner an envelope containing a package of 75 grams of glucose and a box. The box contains four vials for urine and four vials for blood and a set of instructions as to time, etc. After the samples are obtained, the examiner seals the box and mails it to our Home Office laboratory in New York. The blood is preserved with a very small amount of sodium fluoride and mercuric chloride in each vial, and the cases in which glycolysis occurs in transit are rare. On the reverse of the instruction sheet, the time intervals are recorded by the examiner, and there is also a chart for charting the blood and urinary findings at the Home Office, the sheet being returned with the samples. We allow the examiner an extra fee of \$10.00 for obtaining the samples. During the early years, we continued the test through the third hour, but about ten years ago we discontinued the three hour procedure and stopped at two hours, as we did not feel that the third hour observation was sufficiently productive of any important information. In evaluating the risk, we employ a formula which takes into account the behavior of the blood sugar curve during only the second hour, and we consider four types of curve — 1. unfavorable, 2. indeterminate, 3. favorable, and 4. very favorable (renal glycosuria).

The point which I wish to stress is this: During a period of practically twenty years, The Equitable Life Assurance Society has insured glycosurics on the basis of a formula which was at first purely empirical, but the fact-finding element consisted, for all practical purposes, in a standardized uniform procedure. Furthermore, the use of this formula has proven to be satisfactory as a selection method both from the standpoint of the company and of the applicant for insurance. Unfortunately, during the War years, we have been unable to study the experience each year because of shortage of actuarial help, but I have been informed by the actuaries that no noticeable trend has appeared in routine observation of death claims to indicate that our selection method has been unsound. It is anticipated that in the near future a more detailed study will be made which may or may not justify a modification of the formula which has been changed only once in the past. Consequently, I am constrained to emphasize the point that the method of selection which the Equitable has pursued has been sound. In this connection, I would like to comment briefly on a "follow-up" study which was conducted about ten years after we intensively started insuring of glycosurics, viz: in 1934. Naturally, we were not unduly interested, at the moment, as to the outcome of lives still insured, but we investigated the outcome in the cases of individuals whose applications had been declined or who had refused to take the policies offered to them, in order to determine what effect might have been produced on mortality statistics if insurance had been in force on the entire group studied. Owing to restrictions as to expense, clerical help, etc., we attempted only the tracing of in-

dividuals whose name commenced with a letter in the alphabet through K. This produced material amounting to approximately 2200 lives of which about 400 did not take the policies offered and about 1800 were refused insurance. Through various sources, we received information concerning nearly 94% of those investigated, which is obviously a high percentage of results to be expected in a study of this nature. Without going into exhaustive statistics, we demonstrated, with many *conservative* presumptions, the validity of our selective formula in the sense that it rejected beyond question of doubt those who should have been rejected. At the same time, in all fairness, it appeared that we had, in some of the cases where the policy was not taken, charged an unduly high extra premium, and as a result of this study we modified our formula to make it more lenient in its selective operation.

This material was presented by myself as a co-author with Dr. Brathwaite and Mr. Mills of our Actuarial Department, and is recorded in the Proceedings of the Association of Life Insurance Medical Directors, Volume XXIV, 1937.

Parenthetically, and not wishing to get on disputatious ground, I would here interject an item that the insurance companies are well aware of the fact that certain eminent clinicians have recently expressed an opinion that, with the increasing success in the use of insulin treatment, insurance companies could insure diabetics receiving insulin, possibly even at standard rates. Probably the day will come when insuring companies will go into this field, but, at the moment, it appears that some of the specialists who advocate this are not aware of several of the basic restrictions under which life insurance companies operate.

SUMMARY

1. In my opinion, Dr. Mosenthal has made an important contribution to the literature by pointing out the fallacies which have crept into the problem of evaluating glycosuria, and also by advocating the adoption of a standardized procedure using venous blood and a simple, accurate micro method.
2. However, from the standpoint of life insurance medicine, it is important that the procedure be of a sufficiently simple nature so that it can be carried out by a small town practitioner who is not versed in laboratory skill.
3. If not only specialists, but general practitioners, and all insurance companies could be persuaded to use a standardized procedure such as Dr. Mosenthal has outlined, the homogeneity of statistics would be greatly benefitted, and naturally also the welfare of glycosurics.
4. From the standpoint of life insurance medicine, I am not convinced that the capillary blood value as a criterion of the rapidity of insulin mobilization should be entirely abandoned even in spite of Dr. Mosenthal's thesis as to the superior values of venous blood determinations.
5. Again, I repeat, that life insurance companies are entitled to use a measuring rod, within reasonable bounds of accuracy, which will enable them to select risks, based on the general law of averages, in a manner which proves fair to all concerned as judged by their own experience.
6. Lastly, may I reiterate that in my opinion a simple standardized uniform procedure used by both clinicians and insurance companies, is a goal to be greatly desired, but on the other hand, human nature being what it is, it seems highly dubious that such a Utopian state of affairs can be attained in the near future.

Discussion by James J. Short, M.D.

Dr. Mosenthal's plea for the use of methods yielding "true blood sugar" should be heeded. It is probably true that most of us have failed to realize the extent of the false interpretations which may arise from employing the usual methods. To think that a value as high as 70 mg. above the true glucose level may be obtained is indeed startling.

The arterio-venous differences found have been explained in a highly satisfying manner. Diffusion as a factor in explaining these rather bizarre fluctuations has not been previously emphasized to my knowledge, yet it is fairly obvious when pointed out.

Equally obvious but likewise generally overlooked is the importance of arterial blood sugar values in the attempt to diagnose renal glycosuria.

The authors are to be congratulated on a fine piece of research and an excellent discussion of their results.

Editorials

THE CAUSE OF DIABETES IN MAN — A PROMISING ARM-CHAIR PHILOSOPHY

DOCTOR I. ARTHUR MIRSKY has engaged in a very productive form of "arm-chair" philosophy in attempting to answer the question: "What is the Cause of Diabetes Mellitus in Man?" — a question which in the present state of our knowledge cannot be answered. Mirsky has with astuteness assembled a large collection of indirect scientific data to show that pancreatic insufficiency is but one and usually a rather secondary link in the syndrome of diabetes mellitus in Man. This relative or absolute insulin insufficiency is secondary to other factors in the intricate homeostatic mechanism of the endocrine system. Whipple and others gave the old theory of primary pancreatic deficiency the "Coup de grace" when they showed that resection of the entire pancreas in Man produces only a relatively mild form of diabetes which is rather easily controlled with small dosage of insulin. Little wonder that we have been unable to produce in dogs typical human diabetes by pancreatic extirpation when the clinical syndrome as we know it is not produced even in humans by complete pancreatic resection. Mirsky with his usual scholarly approach has resolved the matter into a ratio between demand for and effective supply of insulin. Since insulin is expendable in the body or actually destroyed in the process of performing its function in carbohydrate metabolism, it follows that excessive demands beyond the individual's power to produce must necessarily result in a syndrome of diabetes. Since enormous amounts of insulin have on occasion been recovered from the tissues of individuals who have expired from ketone coma, it must be assumed that this insulin was in some manner rendered inert. Mirsky's theory of trypsin or other proteolytic enzymotic destruction of insulin as an important factor in the genesis of human diabetes is as rational as any concept yet produced and far more probable than most. All that remains is to *prove it*. Nor will his cerebration have been unproductive once his concepts have been proven to be factual, for the same concept will help to clarify the knotty problem of insulin resistance and its relationship to diabetic coma. — *George E. Anderson, M.D.*

WHEN SHALL WE USE GLUCOSE IN COMA?

"SHALL GLUCOSE Be Used in the Treatment of Diabetic Coma?" The answer to this question would seem to be both "Yes" and "No." The time factor, however, is the all-important issue. "At what point of time should glucose be used in diabetic coma?" would seem a more pertinent question. It is obvious that the body in decompensated ketosis is preponderately in obligatory fat metabolism. In the classical picture of diabetic coma the liver is well depleted of its glycogen. Is it to be expected that in this extreme state of insulin insufficiency or insulin resistance the administration of large amounts of glucose will favor a reversal from fat to carbohydrate metabolism? This may be doubted with justification. We know that liver glycogenation and glucose utilization are favored in general by high blood sugar but these normal processes are premised on the presumptive presence of at least some intact insulin function. The negativistic extremely insulin-resistant diabetic-coma patient does not fit into this category of normalcy until at least some ability to function has returned to his overwhelmed insulin mechanism. The effectiveness of parenterally administered insulin is in no little measure influenced by the state of hydration of the body as a whole. Why add more of the offending diuretic glucose when we know that every unutilized or unstored molecule of glucose thus added only promotes the undesirable state of dehydration? The tissues are literally "crying" for fluid.

The first desideratum is re-hydration by electrolytes and fluid. Effective hydration plus early massive insulin administration will usually change the picture of stubborn insulin resistance. When, however, the patient has showed even the slightest ability to negotiate sugar as is evidenced by improvement in the chemical picture, then, and, it would seem, then only should glucose be administered. Glucose is at this time given in sufficiently liberal quantity to force the individual out of excessive and obligatory fat-metabolism and back into carbohydrate metabolism. Gram for gram there is without question in the body of the patient in coma an absolute deficiency in glucose. The glucose which is present is originating from gluconeogenesis possibly as a homeostatic effort to make up for an ac-

tual deficiency. But, the coma patient apparently cannot effectively negotiate even this relatively small amount of newly formed glucose without massive dosage of insulin and liberal hydration. Soskin and Mirsky notwithstanding, why put in more diuretic glucose until the patient gives some indication that he has recovered his ability to handle glucose?

No one would quibble over *small* amounts of glucose relatively early in the treatment — and Peters' dosage might be classed as low. The abuse of glucose is, however, flagrant and unphysiologic. Its abuse not infrequently in grave cases is the straw to break the camel's back.

Stick to the guns, Howard Root!! — *George E. Anderson, M.D.*

ACTA CLINICA BELGICA

THE SECOND world war is ended, and when the curtain rose, all we could see was an entirely destroyed Europe, full of ruins wherever the Nazi regime had reached with its brutality. However, the work of reconstruction has started, and the people in the different countries have gone back to their peaceful work. Medicine, just like all other sciences, has suffered tremendously in these terrible years. It is therefore with the greatest pleasure that we picked up a new journal which has just happened to appear. The brave Belgians, after all their hardships, have settled down and sent us the first issue of their publication, the *Acta Clinica Belgica*. We wish to congratulate the editors, J. Lequime and P. P. Lambert, on their work. It must have been for them like the arrival of a long-awaited child when the first copy of the *Acta* came into their hands. We can hardly realize the difficulties they had to overcome to get material, the paper, and all the other details, to be able to put this journal into the hands of their friends.

We, too, have difficulties in these days with paper, printers, engravers, etc., however, this can in no way be compared to the difficulties in Belgium. The *Acta* shows us that in spite of all their hardships, medical science is again on the way up, that physicians all over

the world are beginning their scientific and practical work of helping suffering mankind.

The *Acta Clinica Belgica* is to continue the "Bulletin de la Société des Hopiteaux de Bruxelles" which reflected the work of this society from 1901 up to 1940. Recently, under the guidance of Dr. Brohée, the Belgian scientific societies have been coordinated into the "Association des Sociétés Scientifiques Medicales Belges."

The *Acta Clinica Belgica* is taking the *Annals of Internal Medicine* and the *Acta Medica Scandinavica and Helvetica* as their examples. Most of their bibliographical notes are from the American medical publications. Among the articles we find one which belongs in the gastro-intestinal field: R. Leclercq, from the Hopital Universitaire Saint-Pierre, discusses "Infiltration Anesthesia in Pains of the Bile Ducts." He describes the intradermal infiltration and the infiltration of the right splanchnic nerve. Besides, he discusses his own method of infiltration of the 12th right intercostal nerve. He found that pains of peritoneal origin and phrenic neuritis were instantly relieved after infiltration. The visceral pains do not appear to be influenced at the moment of injection; however, on the following day, disappearance of functional disorders and gradual disappearance of the visceral sensibility, was observed. All this happens as if this anesthesia blocked certain centripetal paths of reflexes whose answer, whether motor, vaso-motor or secretory, unfavorably modified the functions of the gall-bladder and the bile-ducts. Once this vicious circle is broken, the disorders completely disappear.

So convinced is the author of this fact, that when events do not seem to bear it out, he believes the diagnosis must be revised and that we must investigate the possibilities of an anatomical lesion (gallstones or tumor).

We wish the editors and the contributors to the *Acta Clinica Belgica* good luck and success. Belgian medicine is taking its well deserved place in science and resuming its work.

— FRANZ J. LUST

OBITUARY

DR. HENRY KENDALL of 16 East 96th Street, NYC, who was born in Rumania and brought here as a boy, was a graduate of the Long Island College of Medicine in 1905 and interned at Bellevue Hospital. He was a member of the Long Island College Hospital Alumni Association, American Medical Association, and State and County Medical Societies.

Dr. Kendall was a fellow of the National Gastroenterological Association and one of its founders, and for many years Chairman of the program committee of the National Gastroenterological Association. He has contributed many articles to Gastroenterology and also to aid Ulcer cure. He was a great scholar and possessed many first editions. He was lecturer at the

New York Polyclinic Hospital and a member of the faculty for a number of years and was connected with the Hospital for Joint Diseases. He was also examining physician for the Jewish Theological Seminary.

Dr. Kendall was an elector of the Spanish and Portuguese Temple and was President of the Hebrew Relief Society of this temple. He has given many years of hard work to relief of the poor. Dr. Kendall has two sons, Dr. Milton Kendall of Youngstown, Ohio and Edward P. Kendall of Washington, D. C.

All fellows and members of the entire National Gastroenterological Association will mourn the loss of a great student and teacher.

— WILLIAM C. JACOBSON, Sec.

Book Reviews

Roentgen Diagnosis of Diseases of the Gastro-Intestinal Tract. By John T. Farrell, Jr., M. D., pp. 271 with 190 illustrations (\$5.50). Springfield, Ill., C. C. Thomas, 1946.

This manual is primarily designed for a specific purpose, namely to ground the would-be roentgenologist in the fundamental and general aspects of a broad subject. However, medical students and clinicians will also find it of practical assistance.

The author's wide teaching experience is evident throughout the manual. The arrangement of the text is unique in two respects: first, the close adherence to the standard classified nomenclature of disease; secondly, each disorder is described under headings of changes in contour, alteration of motility, and displacement from the usual anatomical relationships. Not only are the roentgenographic and fluoroscopic signs of the various disorders given, but also included are brief recommendations on the manner of examining that portion of the gastro-intestinal tract to produce the most satisfactory results. The accessory portions of the gastro-intestinal tract are not included in the volume.

The illustrations are clear, well chosen and typical of the various conditions. However, a greater number of plates would have made some of the descriptive text more meaningful. It is a matter of individual opinion, but it seems that an inappropriate amount of space is devoted to foreign bodies in the gastro-intestinal tract, whereas, there is too brief a space devoted to many rather important subjects. Concise description and orderly arrangement make for a certain degree of success in any manual; the medical student and clinician will find these to his advantage here.

Memoirs of Walter Reed: The Yellow Fever Episode. By Albert E. Truby, pp. 239 (\$3.50). New York, Paul B. Hoeber, Inc.

Biographies have on occasion been written to glorify the biographer more than his subject. The story of yellow fever and its conquest as told in this little tome constitutes a tribute to Walter Reed by one of his co-workers. In a style which is simple and restrained, the author tells the story of that long memorable fight against the Yellow Jack. The story of course has been told before, and often, but General Truby's narrative corrects several false impressions and errors in previous accounts. Although Reed and Truby do not seem to have been very close friends, their work brought them into frequent contact. The relationship of the two men was such as to now enable General Truby to give this sympathetic but by no means worshipful account of

his associate's life. This book is enjoyable reading and will probably make a pleasant gift to the graduating medical student or nurse.

Essentials of Histology. By Margaret Hoskins and Gerit Bevelander. Pp. 240 (\$3.50). St. Louis, C. V. Mosby Co., 1945.

This small volume covers the essentials of histologic anatomy adequately for the needs of the college student but will be found too brief for the needs of the medical student. However, it may serve the latter as a handy review and refresher book, particularly as examination time approaches. The very large number of illustrations, taken mainly from student loan collections, are fairly good.

The Physiology of the Newborn. By Clement A. Smith. Pp. 312 (\$5.50). Springfield, Illinois, Charles C. Thomas, Publisher, 1945.

The mystery of the birth process, of "coming into being," has fascinated man since primitive times. The "where from" and the "how" of our ontogenetic arrival has held the attention and imagination no less than has the question of our phylogenetic origin.

The alterations and adjustments of the individual as he begins a new life after birth constitute the theme of this book. The author, who is professor of pediatrics at Wayne University College of Medicine, has written what probably will prove to be an outstanding text. In any event, it is a much-needed book. The physiology textbooks now available cover the adult human physiology adequately, but nearly all have neglected the newborn. In thirteen well-documented chapters, the author has covered the physiology of the child's early life and the changes, both functional and structural, that take place in the transition from fetus to infant.

To the gastroenterologist the chapter on the physiology of the digestive tract will prove of particular interest as will also the chapter on icterus neonatorum. The physician interested in problems of metabolism will find the chapters on heat regulation, mineral and vitamin metabolism, and fetal and neonatal nutrition worth reading. The chapter on neonatal immunology is an excellent summary of the subject.

In several cases the author appears to accept rather uncritically some questionable data, but that is only a minor fault. The book is well planned and well written. Each chapter has a brief clinical summary and a separate bibliography list. Altogether there are 815 references listed. This book certainly should be read by every pediatrician and obstetrician and reading it will also repay the general practitioner.

Diet in Uncontrolled Diabetes Preceding Acute Neuropathy

By

HOWARD F. ROOT, M.D.*

and

CLOVIS CRUZ MASCARENHAS, M.D.*

BOSTON, MASS.

INTRODUCTION

THE FREQUENCY (1) of severe disabling forms of diabetic neuropathy (neuritis) poses a problem in therapy and requires a better understanding of the nature of the disorder. Two cases are presented to permit a discussion of the relationship between carbohydrate utilization and vitamin intake on one hand and the nature of the pathologic chemical and anatomic changes found in this condition on the other. The three patients typify conditions occurring often, not exclusively, in young diabetics in whom occlusive vascular disease is not present, in whom a long course of severe symptoms is followed by complete recovery under appropriate treatment.

Case 1. (21297) Male, aged 42 years, superintendent of schools in a large suburb, retired not for physical reasons but because of independent means. His maximum weight was 280 pounds, height 67 inches, and at the onset of his diabetic neuritis his weight was 245 pounds.

Prior to the onset of his diabetes his diet averaged 5,000 calories per day with between 400 and 450 grams of carbohydrate. This seemed to provide about 1.8 mg. thiamine daily.

In 1934 sugar was discovered in his urine, but as he had no uncomfortable symptoms he paid no attention to the diagnosis and followed no dietary rules, although later he developed typical polyuria, polydipsia and intense hunger.

He came for examination on April 17, 1942 because of development of pain in the legs and hands and particularly the rather sudden onset of marked "pins and needles" sensation in both the hands and feet.

His wife was most intelligent and cooperative. It was possible to get a reasonably accurate summary of his dietary habits during the months when polyphagia and polydipsia were extreme, preceding the onset of his "neuritis" symptoms and this summary with notes is shown in Table I. For extra Carbohydrate, see below.

Notes on Variations in Diet (case 1): For evening meal he would substitute mostly beef, pork, lamb and chicken, each on one day per week. Fish was used only rarely. If at midnight steak was not available he would take 3 or 4 thick sandwiches of bread with cold meat and 15 to 20 pickled onions.

Occasionally he would eat cottage cheese, 120 grams, with cream and butter. He never used salt at all on anything.

Extra Carbohydrate: Apple pie, ice cream, root beer, coffee, soda with added cream and ice cream. While in Florida, he took one quart of orange juice and two pralines at bed time and milk, one pint to a quart between meals.

TABLE I

Vitamin Content of Diets

Case I (21297)

FOOD	Amount in gms.	A I. U.	Thiamine mcg.	Riboflavin mcg.	Niacin mg.	Ascorbic Acid mg.	D I. U.
Orange Juice	360	792	288	108	.79	172.8	-
(Beef, Sirloin) Steak (medium fat)	1920	576	2304	4032	104.8	-	-
(enriched) White Bread	450	-	1080	697.5	9.9	-	-
Butter	150	4500	-	15	.15	-	60
Peas (combination Fresh & Canned)	300	2775	780	390	3.99	51	-
Cauliflower, fresh	300	150	471	557	1.76	240	-
Tomatoes (Fresh and Canned)	300	2775	201	127.5	1.74	67.5	-
Cream, 40%	120	2704	40	176	-	1.6	32
Total Vitamins		14272	5164	6103	123.13	532.9	92

Carbohydrate 518 gms., Protein 572 gms., Fat 469 gms., Calories 8461.

Case II (24229)

FOOD	Amount in gms.	A I. U.	Thiamine mcg.	Riboflavin mcg.	Niacin mg.	Ascorbic Acid mg.	D I. U.
Eggs - 2	100	1000	150	350	.06	-	90
Bacon	45	-	45	60	1.89	-	-
Oatmeal (cooked)	240	-	174	42	.30	-	-
Bread, White, enriched	270	-	648	418.5	5.94	-	-
Orange juice, fresh	150	330	120	45	.33	72.0	-
Butter	100	3000	-	10	0.10	-	40
Milk	2480	4712	1116	4464	1.98	49.6	49.6
Potato	300	74	480	120	2.82	30	-
Meat (beef, sirloin) (medium, fat)	450	135	540	945	24.57	-	-
Peas (combination Fresh & Canned)	300	2775	780	390	3.99	51	-
Total Vitamins		12026	4053	6844.5	41.98	202.6	179.6

Carbohydrate 633 gms., Protein 277 gms., Fat 272 gms., Calories 6088.

Likes and Dislikes: He "hated" dark bread, baked beans and wax beans. He liked only baby lima beans, peas, tomatoes, asparagus, eggplant, Brussel sprouts, cauliflower, lettuce and corn on the cob among vegetables. He had no beer or ale but a cocktail or creme de cocoa twice a week.

No fried potatoes or any foods cooked in deep fat except rarely. Nuts rarely used but he would take pecan pie.

He ate all kinds of cheese except plain American. Very fond of Camembert, Limburger, Roquefort, Swiss, etc.

*New England Deaconess Hospital, Boston
Submitted February 18, 1946.

Did not care for carrots, beets or spinach and ate them seldom. Ate very little cabbage except as Brussel sprouts.

Course of Symptoms: His first urine specimen showed 7.3 per cent sugar and the blood sugar was 300 mgs. Routine Hinton, Wassermann and Kahn blood tests were negative on three occasions. Upon admission to the Deaconess Hospital on April 20, 1942, blood pressure, heart, lungs and abdomen were normal. Within three days the urine was sugar free in most specimens on an insulin dose of 12 units of crystalline and 30 units of protamine zinc insulin with a weighed diet.

During this time he received Vitamin B Complex, 6 tablets a day, and Thiamine. His legs felt stiff and were sensitive even to light touch up to the knees. The numbness of his feet was worse at night and the typical paresthesia continued. After a few days' stay, he went to his home to continue vitamin treatment but returned on May 9 because of the steady progression of the diabetic neuritis. The pain which was worse at night together with the numbness and the paresthesia had become worse and the loss of control in his legs had become marked. The hips and hands were also numb and there was loss of sensation to touch in the feet and loss of sensation to pin point. Vibration sense had gone. Muscle power had practically departed so that he could hardly raise the legs from the bed and within a few days he could hardly turn over in bed. The pain at night was extreme.

Lumbar puncture yielded clear fluid, the total protein was 184 mgs., sugar was 92 mgs. and one white cell. The colloidal gold sol showed 244311+ +00. Hinton-Davies negative.

The application of hot compresses to the legs gave some relief as well as did mild sedatives. He went home May 23 to continue treatment at home, and here his care was most difficult. The pains at night were so extreme that a special tub was set up in the adjoining room and he was carried to the tub for hot baths once or twice during the night to relieve the extreme pain in the legs. He could not stand alone or walk alone. His sedatives included codeine up to 15 grains a day and aspirin up to 125 grains a day. By July 10 the codeine had been reduced to 4½ grains and the aspirin to 50 grains a day. He had begun to walk a little.

On July 27 he was seen with his attending physician because of mental confusion which proved to be due to bromidism. The blood bromide was 280 mgs. He showed papillary eruptions with some pus on the side of the buttock. Edema of both feet was marked. With the omission of the bromide his mental condition cleared promptly and from that time on his improvement was steady. By November 1942 he was able to play tennis.

Development of Neuritis: A striking feature in such severe forms of neuropathy is that once the process begins its progression is rapid and in the developing stage unaffected by the administration of vitamins. Thus during the period beginning April 20 he received vitamins in the form of B Complex, two capsules twice a day, and the treatment of vitamins was continued at home by the addition of Thiamine chloride in 12 mg. doses three times a day. During the period between the hospital discharge when symptoms were present and the time that he returned to the office with a further development of neuritic symptoms his treatment included 4 capsules of B Complex plus 36 milligrams of Thiamine chloride a day. In another such case we would use larger doses. It is evident that the symptoms began at a time when the sugar in both the blood and urine was abnormal, the diabetes uncontrolled and his diet excessive. Relief followed long continued control of the diabetes.

Diabetic Treatment: His diabetes was kept under perfect control at home by the use of insulin and his diet was kept at a constant level of carbohydrate 185 grams,

fat 91 grams, protein 94 grams, calories 1935. His weight steadily fell to 210 pounds. On July 10 the blood sugar was 100 mgs. and the urine was sugar free. He was then taking 8 units of crystalline and 28 units of protamine zinc insulin. Since November 1943 he has not had to take any insulin. On June 15, 1943 the urine was sugar free and the blood sugar at four hours after lunch was 137 mgs. The weight was 213 pounds net. In January 1945 he still was sugar free without insulin and free from symptoms or signs of neuropathy.

Case 2. (24229) Male, aged 41 years, developed typical polyuria in September 1940 and his diabetes was only discovered in September 1942 when in an Army examination glycosuria and high blood sugar were found in a glucose tolerance test. In the four years between 1940 and 1944 his weight fell from 170 to 105 pounds. To use his own words, he could "eat continuously, a whole pie at a time, a pound of candy plus a pound of steak." Polyuria, polydipsia and loss of strength were constant. Muscular weakness was great and painful cramps in the lower legs forced him to get up at night. His memory was bad. Upon admission to the Deaconess Hospital February 2, 1944 his knee jerks were absent, Achilles reflexes were absent, muscle atony and atrophy were marked, skin of the legs was extremely sensitive to touch. The spinal fluid examination showed total protein 320 mgs., no cells, and the blood and spinal fluid Hinton reactions were negative. The spinal fluid colloidal gold test was reported 55543211+0. His first urine specimen contained 7.5 per cent sugar, no albumin, no blood, pus or casts.

The blood sugar was 526 mgs. per 100 cc., blood pressure 84/40. X-rays of the chest and sella turcica were normal, there was no evidence of arteriosclerosis.

In Table I is summarized his diet as obtained after repeatedly questioning not merely the patient, but his intelligent brother, his father and his mother.

With insulin and diet the urine and blood rapidly became normal. Indeed his diabetes proved mild so that on February 28 he required only 4 units of insulin. The fasting blood sugar was 53 milligrams and his diet was carbohydrate 198 grams, protein 93 grams and fat 104 grams. With this treatment and added vitamins, including B complex, thiamine and cod liver oil, his neuritic symptoms improved and a second lumbar puncture gave fluid with total protein of only 177 mgs.

However, after discharge from the hospital weighing of his diet was stopped, control of the diabetes ceased as shown by glycosuria ++ and the following blood sugar values:

Date	Blood sugar (mgs.)	Glycosuria (%)	Insulin
May 22, 1944	538	6.1	24
May 27, 1944	266	4.0	28
April 16, 1945	350	4.6	28

On April 16, 1945 he reported "same terrible pain in legs at night." The symptoms, which improved greatly during his hospital treatment, returned when diet was no longer followed and diabetes was not under control.

Vitamin Content of Diet: In Table I are summarized the estimated contents in various vitamins of the diet of Cases 1 and 2. It is readily admitted that the diet in these two cases varied somewhat from day to day. It is believed, however, that the results presented come much more near to the truth in these patients than has been the case with other attempts made to approximate the diet in diabetic patients whose diabetes has been uncontrolled and whose appetite has been unlimited.

In a comparison of these two diets with the recommended daily allowances for specific nutrients of the Committee on Foods and Nutrition, National Research Council (11), excessive values of vitamins A, thiamine, riboflavin, niacin, and ascorbic acid are seen. Thus for a

man moderately active the allowance is 5,000 units of vitamin A, whereas in Case 1 the estimated amount is 14,272 and for Case 2, 12,026 units. For thiamine the recommended allowance is 1.5 to 2.3 milligrams whereas these two diets contain 5.1 and 4.0 mg. (1 g. equals 1,000 micrograms). The values allowed for riboflavin vary from 2.2 to 3.3 mg. and each received more than 6 mg. Similarly although the allowance in nicotinic acid (niacin) varies from 15 to 23 mg., the values in these two patients' diets exceed the figure greatly. Also the content of ascorbic acid exceeds the allowance of 75 mg. The requirement for vitamin D is less well established in adults but it has been said that it should be present in the diet up to the minimum amounts recommended for infants. The amount of vitamin D in these two diets does seem definitely lower than normal. If an individual like Case 1 deliberately avoids eggs and takes liver only at intervals values for vitamin D may well be low. In general in these two patients an abundance of those vitamins particularly of the B group usually considered of special importance in relation to neuropathy was provided by the diet. It may be remembered that because of the intense glycosuria the amount of carbohydrate actually being metabolized in the body was probably very much lower than would be consistent with the amount of carbohydrate food actually consumed.

DISCUSSION

The assumption that thiamine deficiency, no matter how it was brought about, is an etiologic factor in producing the neuropathy described above in these cases rests upon the hypothesis of an abnormal relation between the thiamine balance and the total non-fat calories of their diet as compared with present day normal standards; secondly, upon the resemblance between the symptoms observed in these patients and the symptoms produced in animals and humans during experimental thiamine deficiency and third, upon the recovery of the patient when the circumstances make possible a return of normal thiamine metabolism. Thus the universal return to normal of all such cases of true diabetic neuropathy in young patients under appropriate treatment begun at a sufficiently early stage makes impossible the belief that the lesion depends upon permanent degenerative changes such as are characteristic of occlusive vascular disease.

The application of the Cowgill calories/thiamine ratio or the Spies and Williams non-fat calories/thiamine ratio to the diets of cases 1 and 2 in the period preceding the onset of neuropathic symptoms leaves no ground for assuming that a thiamine deficiency existed with one exception. If in the period of active diabetes with polyuria, a great loss of thiamine in the urine occurred, then such a deficiency may well have been present. However, there may also have been such a loss of glucose in the urine (Case 1 with glycosuria 7.3 per cent and excretion of 4000 cc. might lose 292 grams of glucose) that the actual amount of carbohydrate metabolized may have been so reduced that the non-fat calorie/thiamine ratio might still have been normal. Indeed it is possible that because of the abnormal carbohydrate metabolism in diabetes a larger intake of thiamine might be needed. Until some quantitative analyses of the actual carbohydrate metabolized and the thiamine balance are obtained, the application of such ratios is difficult.

Is diabetic neuropathy produced by treatment which renders the urine sugar free? In Rundles series (2) of 125 cases the symptoms of diabetic neuropathy such as pain, paresthesia and loss of reflexes developed in 16 per cent after the diabetes was brought under control by means of diet and insulin. It is assumed that by preventing the loss of carbohydrate and thereby increasing the utilization of carbohydrate a thiamine deficiency is brought about. Actually we have never seen a case of true diabetic neuropathy in which the symptoms and the signs did not originate when the diabetes was out of control. Frequently, however, we have found that the history of the time and nature of onset given by the patient is highly inaccurate. Thus the patient remembers only the stage when pain in the leg had become so severe that it was exhausting. It sometimes requires cooperation of the family to bring out the fact that actually pain, weakness and paresthesia began some weeks prior to that period. Then it should be remembered that our knowledge of the duration of a vitamin deficiency necessary to produce muscular weakness, paralysis and atrophy is imperfect. Susan G. Smith (3) produced a progressive ascending paralysis in dogs by feeding a diet free from Vitamin B complex, which could always be prevented by the use of brewers' yeast. She stated that the time of onset of paralysis varied over a long period, from two to eight months on a deficient diet. In human beings the time of development of deficiency symptoms might also vary depending upon how severely deficient the diet was and how adequate for his needs was his previous diet. It is improbable, however, that the severe symptoms of diabetic neuropathy could be produced by changes in carbohydrate utilization which occur during the few days of treatment for diabetic coma. If they are due to deficiencies the deficiencies are of long standing.

The failure of recovery in Case 2 who for a period of a year had received vitamins but had not been under adequate control contrasts strongly with Case 1 in whom a very severe neuritis was completely cured and has remained so during the period when his diabetes was brought under control. If thiamine deficiency is an important factor in diabetic neuropathy it is really dependent upon the metabolic disturbance of uncontrolled diabetes.

Symptomatology: The resemblance between such instances of diabetic neuropathy and well-known thiamine deficiency includes the symptoms and signs related to the periphery. One of the first cases of diabetic polyneuritis attributed to avitaminosis had bilateral foot and wrist drop with recovery (4). Thus the pain, atrophy, loss of power, hyperesthesia, occasional edema, are similar. Loss of memory occurs in occasional cases and anorexia with loss of weight are common symptoms in a severe case with intense pain. Thus Williams and Spies (5) summarize this similarity between thiamine deficiency and diabetic "neuritis" in the following consideration: 1) The well-known relationship between the metabolism of thiamine and carbohydrate. The view has already been expressed by Peters and associates that thiamine functions as a co-

enzyme in the metabolism of carbohydrate and particularly because its combination with phosphate forms a necessary step in the oxidative breakdown of pyruvic acid. Among the mechanisms involved in the oxidation of pyruvate may be mentioned decarboxylation and the other involving oxidation with the production of acetic acid. For a complete summary of pyruvate metabolism in relation to carbohydrate metabolism the forthcoming review of Elmer Stotz should be read.

2) The similarity of the clinical picture, while genuine, may be easily exaggerated. Actually the mental slowness, lack of initiative and loss of memory are not commonly observed as early symptoms in the ordinary diabetic neuritis, although they do occur frequently in diabetic patients who have lost weight and strength during long periods of uncontrolled diabetes.

3) Actually diabetic patients under good control without polyuria or glycosuria do ordinarily have diets with sufficient thiamine content. When, however, the diabetes is uncontrolled, either because it is unrecognized or because the patient does not follow diet, there may be such a disproportion between the carbohydrate and protein calories and the thiamine intake, as well as a loss of thiamine in the urine, that thiamine deficiency may occur. Cowgill (6) has shown that vitamin B₁ deficiency symptoms appear earlier in dogs maintained with a forced water intake than in dogs permitted to drink water as they chose. It should be remembered that in beri-beri the symptoms appear more rapidly when a high carbohydrate intake in the diet is used. However, in beri-beri cardiac dilatation is a common characteristic feature and this rarely, if ever, occurs in diabetic neuritis. The relation of diabetic neuritis and thiamine metabolism is discussed by Needles (7). He found in seven cases of diabetic neuritis that no improvement of the neurologic findings occurred when thiamine was given.

Fein, Ralli and Jolliffe (8), on the contrary, found that in nine cases all were helped by the use of thiamine. They attributed a contributory role in the pathogenesis of diabetic neuritis to vascular disease when they state that owing to defect in the blood supply in the peripheral nerves a greater intake of vitamins is needed to supply the tissues adequately. In general it may be said, however, that in severe cases with actual paralysis and muscular atrophy in addition to pain and loss of reflexes, recovery has only taken place when diabetic control with adequate insulin and a well balanced diet was maintained for many months as well as the use of thiamine.

Pathology: It must be said that many patients with diabetic neuritis examined at postmortem have shown very slight changes in either the spinal cord or the peripheral nerves. However, Wilder found in cases examined pathologically patchy areas of degeneration, more marked distally, and associated with thickening of the walls of the nutrient vessels and considered that therefore arteriosclerosis was an important finding.

There can be no doubt that such changes are found in many diabetic nerves and actually that they are found in many diabetic nerves in patients where no such clin-

ical picture as the acute neuritis we have described has been present. A comparison of this picture with a description of the specific lesions of thiamine deficiency may be made by consulting the description given by McLester (9): "The earliest manifestations of thiamine deficiency are extremely vague; mental depression, lack of initiative, irritability, easy exhaustion, digestive discomfort and pain in the muscles. The most constant anatomic lesions in outspoken disease are, in the order of their frequency, peripheral neuritis, myocardial disease and general edema. The neuritis characteristically begins in the more distal nerves, involving first those of the lower extremities and later those of the upper extremities. Degeneration is usually most marked in the sciatic nerve and its branches. These changes are not limited to the peripheral nerves, for similar alterations have been described also in all tracts of the spinal cord, especially in those in the posterior columns. Likewise, the cranial nerves, notably the phrenic and vagus nerves and also the nerves of the sympathetic system are sometimes involved. There may be any degree of nerve change, from a scarcely recognizable microscopic alteration to complete degeneration with disappearance of both myelin sheath and axis-cylinder."

This description does not limit the lesions to the peripheral nerves and indeed is more consistent with what we observe in clinical patients; namely, symptomatology clearly pointing chiefly to the central nervous system rather than to the peripheral nerves for its cause. It is easily understood that a diabetic "neuritis" may be entirely reversible if these changes have not progressed beyond the early stage.

The frequent involvement of the upper extremities, the spinal cord, the cranial nerves, led Jolliffe (10) to conclude that such patients had a severe or essential neuritis.

That the lesion in the central nervous system is a prominent feature of the pathology is indicated by examination of the spinal fluid of diabetic patients at the Deaconess Hospital summarized in the following table. It will be noted that this table includes many patients who have lesions other than diabetic neuritis. The entire series is analyzed here in order to give the findings in patients with typical diabetic neuropathy against the background of spinal fluid examinations in diabetic patients as a whole.

In 66 patients with atypical diabetic neuropathy 72.7 per cent had values for the protein of the spinal fluid above 51 milligrams per 100 cc. In the other 27.3 per cent, of 18 cases, the neuropathy was extremely mild, consisting of paresthesia, absent knee jerks, but very little pain and no paralysis.

In one hundred cases with other lesions of the central nervous system including tabes dorsalis, cerebral hemorrhage, tumors, etc., abnormal increases in total protein were present in 81 per cent. In 96 patients who had surgical lesions of the feet 50 per cent of them had protein values above normal. These latter patients demonstrate the neurologic lesions important in relation to surgery; namely, anesthesia in the feet.

As a result of this anesthesia the patient with a slight traumatic lesion continues to walk upon the foot until infection penetrates deeply and the patient is finally admitted with osteomyelitis or even infectious gangrene.

The surprising fact that in the syphilitic group 77 per cent showed normal figures is due to the exclusion of patients who had tabes or dementia paralytica. The diagnosis of syphilis rested upon the history and a positive blood Hinton reaction only.

TABLE II

Total Protein in the Cerebro-Spinal Fluid in 280 Diabetics

Spinal Fluid Protein mg. %	Diabetic Neuropathy Cases %		Other Lesions of Central Nervous System		Surgical Lesions of Feet		Syphilis		Miscel.	
up to 50	18	27.3	7	19	48	50	7	77.8	60	82.0
51 to 75	22	33.3	7	19	30	31.3	2	22.2	13	18.0
76 to 100	13	19.7	12	34	12	12.5	-	-	-	-
101 to 300	12	18.2	7	19	6	6.2	-	-	-	-
301 to 5750*	1	1.5	3	9	-	-	-	-	-	-
Total - 280	66	100.0	36	100	96	100.0	9	100.0	73	100.0
Normal figures	18	27.3	7	19	48	50	7	77.8	60	82.0
Over	48	72.7	29	81	48	50	2	22.2	13	18.0

*The highest figure was 5,750 mg. in a case of meningitis.

†Including cerebral hemorrhage and thrombosis, meningitis, tumors primary and metastatic, tabes, etc.

In the miscellaneous group are included those patients where the symptoms were vague and no definite diagnosis was finally made.

If the group of patients with diabetic neuropathy is now analyzed according to the level of protein in the spinal fluid it is seen that 53 per cent of the group had values between 51 milligrams and 100 milligrams per 100 cc. The high values from 101 to 300 milligrams included 12 patients with very severe diabetic neuropathy who received intensive treatment for long periods of time in the hospital, usually because they were paralyzed and suffering intense pain. Doses of thiamine given by needle, intravenously or under the skin, up to 50,000 units daily did not produce any prompt effect. However, those patients did recover with few

exceptions. With the highest values the condition seemed to be, in some instances, not so reversible as in the lower levels.

CONCLUSION

1) Diets excessive in calories and vitamins were taken during the period preceding onset of acute diabetic neuropathy in one case with recovery and in a second case with relapse which followed failure to continue treatment with diet and insulin.

2) In uncontrolled diabetes the total caloric intake may be greatly in excess of utilization. In such cases if the diabetes is fundamentally mild and no complications such as infection or other endocrinopathies are present, ketosis may not occur for a long period. However, hyperglycemia, loss of weight and severe neuropathy may result even though the intake of vitamins is large. The role of relative vitamin deficiency is difficult to assess without accurate measurement of carbohydrate oxidation and of vitamin balance. It is not the severity of the diabetes but the lack of control by diet and insulin which underlies neuropathy.

3) In true diabetic neuropathy the administration of excessive amounts of thiamine or other vitamins, without therapeutic control of diabetic metabolism does not suffice to bring relief to severe cases. In uncontrolled diabetes failure of absorption of vitamins, utilization or excretion of the urine may produce a deficiency. In such patients, particularly after diabetic coma, the administration of vitamin B complex should be begun promptly.

4) The findings in the cerebro-spinal fluid in diabetic neuropathy, including an increase in total protein, absence of cellular inflammatory reaction, and a change in the colloidal gold test, strongly indicate that the central nervous system is the chief site of the lesion in diabetic neuropathy. The condition is not a peripheral neuritis.

5) The failure to obtain prompt improvement is usually due to the fact that diabetic treatment has been begun too late, sometimes even after irreversible changes have occurred. The common causes of failure are dietary excesses (including protein and fat as well as carbohydrate) and failure to control the diabetes by a proper combination of diet and insulin.

REFERENCES

1. Joslin, E. P., Root, H. F., White, P. and Marble, A.: *Treatment of Diabetes Mellitus*, 7th Ed., p. 489, Lea & Febiger, Philadelphia, Pa., 1940.
2. Rundles, R. W.: *Diabetic Neuropathy*, *Medicine*, 24:111, 1945.
3. Smith, S. G.: *Progressive Ascending Paralysis in Dogs due to Deficiency of a Vitamin B Complex Factor found in Yeast*, *Science*, 100:389, Oct. 27, 1944.
4. Root, H. F.: *Med. Clin. North America*, 5:1433, 1922.
5. Williams, Robert R. and Spies, Tom D.: *Vitamin B and its Use in Medicine*, MacMillan, New York, 1938.
6. Cowgill, G. R.: *Vitamin B Requirement of Man*, Yale University Press, New Haven, 1934.
7. Needles, William: *Vitamin B₁ Therapy in Diabetic Neuritis*, *J. A. M. A.*, 121:914, March 20, 1943.
8. Fein, Harry D., Ralli, Elaine P. and Jolliffe, Norman: *J. A. M. A.*, December 7, 1940.
9. McLester, James S.: *Nutrition and Diet in Health and Disease*, W. B. Saunders, Philadelphia, London, 1943.
10. Jolliffe, Norman: *Diagnosis, Treatment and Prevention of Vitamin B₁ Deficiency*, *Bull. N. Y. Acad. Medicine*, 15:469, 1939.
11. Bowes and Church: *Food Values of Portions Commonly Used*, 5th Edition, p. 7, 1945.

Fasting Blood Sugar vs. Postprandial Blood Sugar as Observed in Normal Individuals, Medical (non-diabetic) Patients, and Patients with Diabetes.

Special references to: plain, protamine zinc and globin insulins, compatible hyperglycemia and arteriosclerosis.

By

ANTHONY SINDONI, Jr., M.D.*

PHILADELPHIA, PA.

ONE WILL OBSERVE upon review of the literature on diabetes that common practice among physicians in guiding their diabetic therapy — diet and insulin (plain insulin and protamine zinc insulin) — is to base it upon fractional or 24 hour urine for examination of sugar content or upon the blood sugar of the patient before a meal. These methods of determining the state of the diabetic's carbohydrate metabolism have been in effect for many years, being used even before the discovery of insulin. But as guides to correct the disturbed metabolism of a diabetic, they have been far from completely successful. True, to a measurable degree, diabetic coma has been conquered and the life expectancy of a diabetic increased by insulin and diet, but vascular complications are increasing as well as their resultant invalidism and heightened mortality rate.

That vascular complications of diabetes are increasing became evident to us from our observation of the augmented number of diabetics sent for admission to our Metabolic Service suffering from such cardiovascular complications as gangrene, coronary disease and eye affections such as cataract and retinitis. These complications of diabetes have contributed to increase invalidism as well as the mortality rate. Thus in the year of 1944 the total number of patients with diabetes admitted to the Metabolic Ward was 471: 180 males, 291 females. Of this group, 70 patients had amputations as a result of gangrene — 41 legs and 29 toes; and 99 deaths occurred from diabetes for the year (approximately one death out of every 5 admissions). At present we have 1,239 active diabetic patients coming at regular intervals to the clinic for periodic check-up of their condition.

It was noted that upon admission many patients, because of insufficient income to maintain themselves on an adequate diet, suffered from various nutritional disturbances which helped to aggravate their diabetes as well as to precipitate various complications. These latter observations were first made in one of our diabetic clinics where we found that an entire group of 85 diabetics suffered from vitamin deficiency (1). When these patients were placed upon an adequate diet, improvement in their physical condition resulted in all cases, and in a large percentage of cases a reduction or discontinuance of insulin dosage resulted.

Observations have revealed that severe arteriosclerosis and a high incidence of cardiovascular abnormalities other than retinitis tend to occur in patients with diabetes (2). Thus, for all ages Root and his associates (3) have found coronary occlusion to occur in 32 per cent of their diabetic patients as compared with 6 per cent of non-diabetic patients. Nathanson's (4) observations in 100 autopsies found severe coronary disease in 41%; above 50 years the incidence was 52.7% as compared with 8% in even a larger series of non-diabetics of the same age. Of the total number of 1579 diabetic deaths studied in Philadelphia from 1940 to 1942 inclusive, 707 deaths or 44.8% were caused by arteriosclerotic complications (5). In 120 cases of diabetes in persons above the age of 39 years, arteriosclerosis was found in the aorta in 75 per cent of the patients, in the retinal arteries in 69 per cent, in either the aorta or the retina in 89 per cent, and in both in 51 per cent (2). It was also observed in these studies that nine-tenths of all diabetic patients have attained ages at which they are exposed to the dangers of arteriosclerosis from causes other than diabetes. However, O'Brien and Allen's (6) findings for age appear to differ. They found an incidence of diabetic cataract in almost 14 per cent in 260 diabetic patients under the age of 21 years. In a survey of the fundi of 555 diabetic patients they found that diabetic retinopathy occurred in 4% of the patients with diabetes under the age of 31 years. They also report a previous encounter with a case of retinal hemorrhages in an 11 year old girl having well developed lipemia retinitis.

Lisa and his associates' (7) post-mortem studies between January 1, 1928 to December 31, 1941 of 193 patients with diabetes mellitus revealed that sclerotic changes increase in frequency as age advances occurring ten years earlier than in patients without diabetes. They found in their original series of 193 diabetic patients coronary involvement in 138, and concluded that occlusive accidents in the coronary arteries of patients with diabetes was of greater frequency at all ages than in those without diabetes. However, the frequency of the coronary accidents was not correlated with age; and severe arteriosclerosis is more frequent at all ages in persons with diabetes.

Eisle (8) was able to make a study of the juvenile diabetic patient twenty years or more after the onset of the disease. These individuals lived before the discovery of insulin. From his studies of 73 patients with diabetes of twenty years (i. e. until March 1, 1942)

*Chief of the Department of Metabolism, Philadelphia General and St. Joseph Hospitals, Chairman Advisory Committee on Diabetes to the Director of Public Health, City of Philadelphia.

arteriosclerosis was found to be the earliest and the most important complication, 30% revealing peripheral arteriosclerosis roentgenologically, 55% having moderate to advanced ocular arteriosclerosis, while 70% had either hypertension or albuminuria or both at an average of 29 years in addition to arteriosclerotic changes.

Of special note are the observations made by Laipply and his coworkers (9). They found, in post-mortem studies, a marked association of glomerulosclerosis with diabetes. Their studies revealed intercapillary glomerulosclerosis an uncommon lesion in non-diabetic persons, to be common in cases of diabetes, occurring in 63.7 per cent. They also noted renal lesions and hyalinization of the islets in 63.1 per cent. They found that neither the degree of diabetes nor its duration bore any relation to the degree of development of glomerulosclerosis. They also described the case of a 16 year old white girl with severe diabetes of ten years duration with the typical renal lesion. They conclude from their findings that the renal lesion is the "most reliable criterion available for the post-mortem diagnosis of diabetes mellitus."

Observations (10) in the period of 1930-1938 in a series of 155 deaths of patients with diabetes revealed that the primary cause of death was gangrene of the leg in 21.3% of the cases; myocardial degeneration in 11.7%; cerebral vascular disease in 9.7%; acute coronary occlusion in 5.2%; diabetic coma in 3.9%. It is interesting to note that cholelithiasis was found in 27.6% of the cases as compared with its presence in 11.0% of general medical deaths.

The percentage increase in the mortality from diabetes for the total United States in 1940-1942 as compared with 1930-1932, was 27%; for the state of New York, 40%; Pennsylvania, 45%; New Jersey, 42%; Oklahoma, 48%; California, 19% (11).

Experimental Observation

Because of both increased diabetic cardio-vascular complications and mortality rate we decided to make a clinical investigation of their relationships to so-called "adequate diabetic control." As to the examination of fractional or 24 hour urine for sugar estimation in guiding diabetic therapy, we have found through a careful study that this method may be misleading (12). A knowledge of the blood sugar levels obtained during the patient's normal activities is a much better index of the patient's carbohydrate metabolism. For this reason we have confined our experimental observations to blood sugar studies.

Realizing that the common practice of many physicians is to examine the blood of the diabetic before a meal in order to determine the degree of his disturbed blood sugar level, we decided 1) to determine the blood sugar level of a group of normal individuals before a meal, 2) to examine the effect of an every day or an average "normal" meal — preferably breakfast — upon the blood sugar level of these normal persons. We avoided the glucose tolerance examination because we felt that it was an artificial strain upon the carbohydrate metabolism and not a true measure of the patient's metabolizing power for food. We are interested

in elements of food vital to man, necessary to carry on the normal physical duties of every day life since a mixed diet calls into function more of the various organs of the digestive apparatus. We agree with Soskin (13) as to the true significance of the dextrose tolerance test. He is of the opinion that it is often sadly misinterpreted, and that the amounts of sugar orally administered, being usually larger than those ordinarily encountered in feeding, merely impose an artificial strain upon the regulating mechanism. 3) to make blood sugar studies similar to those made in the normal group with a group of patients suffering from various pathological disorders (medical) but not from diabetes. 4) Finally, to make similar blood sugar studies in a group of diabetics. All the members of the various groups were placed upon the same diet for these studies to enable us to interpret better the changes in the blood sugar.

Thus the test breakfast consisted as follows:

Grams	Household Measures	P.	F.	C.
200 Orange Juice	1 glass	2.	0	21.6
18 Cornflakes	½ cup	2.	0	18.
60 20% cream	¼ cup	2.	12.	2.
10 sugar	2 tsp.	0	0	10.
2 eggs (scrambled)	2 "	12.	12.	0
30 bacon	3 strips	6.	18.	0
24 butter	2 pats	0	20.	0
60 bread	2 slices	7.	0	31.
coffee	1 cup	0	0	0
10 sugar	2 tsp.	0	0	10.
		32.	64.	95.6

Examination of the blood for glucose content was made according to the Folin-Wu method. Specimens of blood were obtained from the subjects in the fasting state. Then a specimen of blood was obtained every ½ hour for two hours as well as the third and fourth hour after they had eaten the test-meal or breakfast, making a total of seven separate blood-sugar examinations for each patient. The age of the normal subjects varied from 6 to 61 years. The specimens of blood were obtained while the individuals were carrying on their routine activities. These normal individuals comprised resident physicians, dietitians, social service workers, technicians and other employees of the hospital, and a six year old boy who was so kind as to submit to the test while visiting a relative.

In TABLE I are tabulated the results of the meal tolerance upon the blood sugar levels of the normal individuals.

The results of the breakfast revealed no rise of the average blood sugar level at the end of the first 2 hours of the 30 minute intervals and of the second 2 hours 60 minute intervals after the meal as compared with the blood sugar level (fasting) before the breakfast with the exception of .8 mg. rise at the end of the first ½ hour post-prandially. Following this insignificant rise of the average blood sugar, a drop below the fasting level became evident throughout the 3½ hour post-prandial period.

In the individual patients we noted two instances in which the post-prandial blood sugar level descended below 70 mg., one at the end of 30 minutes and the

other at the end of 60 minutes interval. Both blood sugar levels were 67 mg.

Post-prandial blood sugar levels above 100 mg. were found in 7 instances. The highest level, 117 mg., occurred at the end of the first 30 minutes in only one patient. However, following this latter rise a descent below 100 mg. was maintained throughout the remaining post-prandial interval of 4 hours with the exception of a blood sugar level of 102 mg. at the end of the 4th hour.

In two other patients the blood sugar level at the end of 30 minute interval was respectively 104 mg. and 109 mg. In the former patient following a 30 minute interval the blood sugar level dropped below

few of the patients because of their condition had been confined to the hospital for many years, and others for only a short period. We felt that patients with chronic ailments of long duration would make good subjects for our study of their carbohydrate metabolism as affected by the so-called average meal. The age of the group varied from 15 years to 67 years. The individuals suffered from pathological disorders such as pulmonary T. B., cancer, hemiplegia, gall-bladder disease, syphilis, etc. as indicated in the table. The results are tabulated in TABLE II.

A rise in the average blood sugar from a fasting level of 90.1 mg. to 120.4 mg. was noted at the end of the first $\frac{1}{2}$ hour post-prandially. A drop in the blood

TABLE I
Normal (Non-Diabetic) Meal Tolerance

Initial of Patient	Age of Patient	Weight	Sex	Fam.	1/2 hour	Blood Sugar Level mg/100 After Breakfast					Comments
						1 hour	1 1/2 hours	2 hours	3 hours	4 hours	
R.S.	47	150	F	92	98	115	115	112	114	115	
M.K.	51	205	F	103	116	89	96	98	91	96	
A.C.	28	118	F	37	76	73	90	87	102	90	
B.S.	25	120	M	87	97	12	10	83	12	17	
H.S.	22	149	M	89	16	74	77	17	17	12	
H.P.	56	134	F	91	97	92	90	11	98	96	
K.R.	27	136	F	83	78	77	14	13	19	91	
P.H.	36	140	F	91	91	12	17	16	16	94	
M.C.	16	114	F	82	79	27	73	15	12	79	
B.G.	19	162	F	92	117	92	78	15	92	102	Took thyroid extract to reduce 2 months previous
H.P.Jr.	24	136	M	89	91	98	94	19	93	97	
J.M.	40	126	M	91	104	76	12	76	19	91	
K.K.	36	200	M	98	104	102	93	17	19	17	
K.R.	61	141	M	91	98	102	91	19	102	100	
M.E.	6	51	M	86	12	12	15	16	93	92	Sister has diabetes
A.E.	11	68	M	92	17	15	16	15	11	92	Sister has diabetes
E.D.	11	72	F	87	11	79	13	13	14	17	
K.A.	16	113	M	102	15	15	19	91	91	11	Brother, Sister are diabetics
J.F.	13	126	F	100	100	14	92	94	94	19	Sister has diabetes
A.M.	26	124	F	86	15	78	12	13	93	11	
Average	30.5	138		91	91.1	84.4	85.6	16.2	19.2	90.1	

100 mg. which level was maintained throughout the post-prandial period, whereas in the latter patient at the end of the first hour the blood sugar level descended to 102 mg. However, at the end of 90 minutes the blood sugar concentration dropped to 93 mg. and remained below 100 mg. throughout the post-prandial interval. In another patient the blood sugar rose from a previous low level of 98 mg. at the end of 30 minutes to 102 mg. after the first hour. At the end of $1\frac{1}{2}$ and 2 hours the blood sugar concentration descended to 91 mg. and 89 mg. respectively, to rise again to 102 mg. at the end of 3 hours; whereas at the end of 4 hours the blood sugar level dropped to 100 mg.

Graphically illustrated, the average post-prandial blood sugar levels for the various intervals noted, showed a drop at the end of the first hour with a slight rise thereafter approaching the fasting level at the end of the 4th hour.

Similar blood sugar studies were made with the test meal in a group of patients suffering from various non-diabetic diseases (medical), throughout the hospital. A

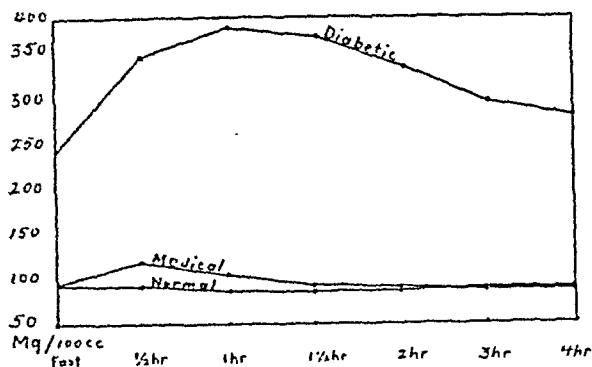
sugar level to 107.5 mg. was noted at the end of the first hour a drop which continued throughout the remaining post-prandial interval, with the exception of a slight rise from a level of 86.1 mg. to 88.4 mg. at the end of the 4th hour. But in spite of the highest rise of 120.4 mg. and 107.5 mg., the blood sugar levels were below 100 mg. throughout the remaining post-prandial interval.

In the individual medical patients, the rise in the blood sugar level became most apparent during the first $1\frac{1}{2}$ hours after meals, whereas in the remaining intervals of the 4 hour period the blood sugar levels dropped below 100 mg. with exception of three patients who had blood sugar levels of 107 mg., 102 mg., and 100 mg. at the end of 2 hours post-prandially.

In the interval when the blood sugar rise became most apparent — first $1\frac{1}{2}$ hours post-prandially — we observed the highest blood sugar levels at the end of the first 30 minutes in 3 patients: 150 mg., 152 mg. and 154 mg. respectively. However, in these same patients we noted a decided drop in the blood sugar level

following the next 30 minutes interval. We did observe the lowest blood sugar level of 63 mg. and 64 mg. at the end of 2 hours in two separate patients. These blood sugar levels were lower than the 67 mg. observed in the normal person (Graph No. 1).

Graph 1 Meal Tolerance



val at the end of the first hour as compared with those of the normal persons were approximately the same. It appears from the constancy of the post-prandial blood sugar levels that the various pathological disturbances as well as the patients' inactivity had practically no effect upon their carbohydrate.

Interpretation of the blood sugar level of normal and medical (non-diabetic) patients.

(a) *Mode of Control of the Normal Blood Sugar*

The above blood sugar studies of the normal and medical (non-diabetic) patients corroborate the early work of Claude Bernard (14) up to the more recent studies of Mann and Magath (15) that noted fatal hypoglycemia in animals following hepatectomy; that the liver is the organ chiefly concerned in the maintenance of the normal blood sugar level. These laboratory studies demonstrated that the source of blood sugar is liver glycogen. However, the origin of liver glycogen is not only carbohydrate food but non-carbo-

TABLE II
Medical (Non-Diabetic) Meal Tolerance

Initial of Patient	Age of Patient	Weight	Sex	Fast.	Blood Sugar Level mg/100 After Breakfast						Complications
					½ hour	1 hour	1 ½ hours	2 hours	3 hours	4 hours	
C.W.	63	144	M	78	100	115	111	107	91	89	Fever of unknown origin, primary or secondary Ca of liver; hospitalization 1 mo.
W.R.	61	113	M	85	118	129	107	98	85	82	Hypertensive C.V. disease; enlarged liver; hospital 1 month
E.B.	67	93	F	81	154	120	93	76	76	83	Hypertensive C.V. disease; cardiac decompensation
M.D.	15	118	F	90	126	107	103	95	86	82	Rheumatic heart disease; pulmonary congestion. Hospital 1 month
H.R.	23	173	M	89	75	85	86	81	72	94	Glycosuria of 2 yrs.; mother also has glycosuria; non-diabetes.
P.A.	39	144	F	96	82	81	90	88	86	89	Pott's disease, spastic paraplegia, congenital syphilis; present stay in hospital 21 years.
J.W.	58	145	F	88	108	102	102	88	97	88	Left cerebral thrombosis, right hemiplegia; hypertensive C.V. disease, hospital stay 8 years.
H.D.	57	98	F	97	152	110	100	102	93	89	Osteitis deformans — "Paget Disease."
I.T.	25	120	F	86	120	105	89	87	87	86	Bilateral Fibro-ulcerative pulmonary T. B.
C.U.	58	143	M	91	141	139	92	80	78	89	Left cerebral thrombosis, right hemiplegia; 3 years in hospital
J.S.	46	100	M	91	150	120	84	63	85	93	Marie's Hereditary Cerebellar Ataxia. Dental caries, traumatic injured knee; 10 years in hospital
A.P.	40	120	M	91	104	76	82	76	89	91	Bilateral Fibro-ulcerative pulmonary T. B. Hospital 5 months
A.G.	55	116	M	80	137	129	111	93	96	89	Bilateral Fibro-ulcerative pulmonary T. B.; T. B. for 20 years
S.J.	55	308	M	104	104	103	87	64	78	82	Gout; obese
A.M.	55	177	M	105	136	92	103	109	93	100	Acute exacerbation of chr. cholecystitis cholelithiasis, with jaundice which subsided in few days.
Average	47.3	140.7		90.1	120.4	107.5	96	87.1	86.1	88.4	

Graphically illustrated we note an approximation of both blood sugar levels of the medical and normal persons at the end of the 2nd to the 4th hour. The parallelism of both groups of blood sugar levels occurred subsequent to the first 1/2 hour post-prandially when a drop of the blood sugar was noted.

The total average blood sugar levels for the various intervals of the medical patients with exception of the rise of 120.4 mg. and 107.5 mg. in the 30 minute inter-

hydrate food as well. This latter source of carbohydrate is well described from Holmes' (16) classification of non-carbohydrate material — "(a) protein; (b) fatty acid and (c) small molecules which may arise in the course of metabolism from various sources." Osborne and Mendel (17), Tsai and Yi (18), and many others (19-25) have observed that a variety of non-carbohydrate food can serve the liver as material for glycogen as well. Although the origin of glycogen

from protein has been accepted for some time (26), its source from fatty acids as well has been accepted by various laboratory workers upon evidence that the anterior lobe of the pituitary contains some factor or factors responsible for the conversion of fat to carbohydrate (27, 28).

The factors, or the mechanism, affecting the liver glycogen so as to maintain the constancy of the blood sugar level before meals when there is no absorption of food from the gastro-intestinal tract as well as following the ingestion of food when there is much absorption, as our observations show, has aroused much controversy. However, one cannot help but conclude when he observes the lowered blood sugar concentration rapidly return to normal following the ingestion of soluble sugar that carbohydrates are the most rapidly absorbed and easily metabolized of foodstuffs. The studies of Bock and his associates (29) observe an initial rise in the blood sugar concentration as early as 3 minutes following the ingestion of 110 grams of glucose in solution. Foster (30) speaks of instances in which the blood sugar concentration (venous) rose and returned again to normal within 30 minutes after ingestion of glucose.

Newton (23) is of the opinion that the rate of removal of sugar from the blood is governed in some way by the needs of the body and in no way directed towards blood sugar regulation — apparently a process which can be accelerated or retarded. Some investigators (31) claim that the percentage amount of sugar present in the blood is not a fixed quantity even in health and that the variations occurring are limited to a comparatively narrow range. They also claim that the most important factor affecting the percentage amount of blood sugar at any particular interval is the ingestion of food. Cori (32) is of the opinion that the blood sugar curve is the resultant of several metabolic processes all going on simultaneously at an unknown rate. Folin and Berglund (33) apparently regard the blood sugar level as an index to the rate of glycogenesis. They believe it is the tissue absorption of sugars from the blood rather than glycogen formation that is responsible for the sugar's failure to accumulate in the blood. Newburgh and Conn's (34) account for the rapid removal of dextrose from the blood stream is oxidation of dextrose and its deposition as glycogen.

However, there appears to be much confusion in trying to explain the constancy of even insignificant reduction in the blood sugar level during the absorption of the food as observed in our studies. Chambers (35) claims that blood sugar changes reflect the rate and not the nature of glucose utilization. Foster (30) claims that the rise and fall of the blood sugar is dependent on "the relative velocities of the inflow of glucose from the intestine and its subsequent removal from the blood stream by the tissues." His explanation for the hypoglycemic phase of the curve is in agreement with Frank (36), McLean and de Wesselow's (37) hypothesis — "that the ingestion of glucose causes over-activity of the glycogen-forming mechanism." The excess sugar

in the circulation is the stimulant for the mechanism which deals with the sugar. McLean and de Wesselow claim it to be glycogen synthesis, largely in the liver. Cori (32) found a variation in rate of glycogen deposition due to unequal absorption but to the effect of preceding starvation in the liver. Experimental evidence also revealed that insulin secretion is at a low ebb during starvation.

Cori (38) is of the opinion that there is an enzymatic hydrolysis of glycogen in the liver and to subsequent conversion to lactic acid in the muscle that leads to the formation of blood sugar. He feels the enzyme activity in the cell is influenced by various substances — insulin, epinephrine, adreno-cortex, anterior pituitary hormones and others.

Houssay (39) claims that the liver governs the blood sugar level under the influence of hormone equilibrium with the pancreas having a fundamental part in maintaining a normal blood sugar level by preventing its increase and influencing the production and consumption of glucose through its insulin secretion. He contends that the level of the blood sugar governs the secretion of insulin, and vice versa. This latter thought also forms the basis of Jordan's (40) experimental observation which supports the hypothesis "that incoming glucose acts as a stimulus to the islands of Langerhans, provoking a mobilization of insulin and thereby increasing the sugar-using power (tolerance) of the organism." Soskin and his co-workers (41) inferred from laboratory observations that normal dextrose tolerance curves can be maintained in depancreatized dogs as long as there is sufficient circulating insulin to keep the blood sugar level constant. Soskin and his associates' (42) observations on the dextrose tolerance curve suggest "that whenever the blood sugar tends to rise above the normal level, the liver responds by diminishing its output of sugar to the blood. The stimulus which elicits this hepatic inhibitory response is the blood sugar itself, and the threshold of stimulation of the hepatic mechanism in a particular animal coincides with the level of blood sugar which that animal habitually maintains. It is suggested that this mechanism is chiefly responsible for the characteristic dextrose tolerance curve when sugar is administered to the normal animal. The influx of exogenous sugar into the blood stream raises the level of the blood sugar above the threshold of stimulation of the homeostatic mechanism. The liver promptly curtails the supply of sugar which it has been pouring into the blood. The exogenous sugar thus temporarily replaces the supply from the liver. Utilization and storage rapidly return the blood sugar toward its normal level, whereupon the liver resumes its secretion of sugar." The claim is made that their results yield direct and quantitative evidence of the homeostatic regulation of the blood sugar level by the liver.

This view, however, is in contradiction to Cori (32), who holds that the extra insulin or increased insulin secretion of the pancreas is caused by the administration of dextrose and is responsible for the normal dextrose tolerance. This view of extra-secretion of insulin

caused by extra-carbohydrate to maintain a normal blood sugar curve is also shared by Williams and Dick (43); Holt and Greisheimer (44); Deuel and Gulick (45). In Cori's opinion a regulatory mechanism is set into motion when the blood sugar level is increased or decreased. When the blood sugar is increased, extra secretion of insulin is given off while a decreased blood sugar causes an increased secretion of epinephrine to be discharged. Thus he feels the action of two hormones on blood sugar production and utilization is closely associated with the mechanism of blood sugar regulation. The disappearance or reduction of blood sugar he claims is dependent upon its oxidation in the tissues and on its conversion into glycogen and fat; also under certain conditions he claims sugar is lost from its excretion in the urine. Soskin and his associates (41), however, hold the belief that the normal liver is the major factor in determining the normal dextrose tolerance and not necessarily an extra secretion from the pancreas. They contend from their observations that in the presence of sufficient insulin, not necessarily extra secretion, the normal liver as one of its reactions to administered dextrose, decreases its sugar output to the blood which it has been supplying from its own resources. They claim this normal glycogen function of the liver is under the influence of proper endocrine balance. It is the presence of the normal liver that is essential and not the pancreas to the metabolic reactions which determine the normal dextrose tolerance curve. Himsworth (46), however, takes exception to Soskin's homeostatic theory. Although Soskin's theory gives many explanations of hepatic functions, he feels it does not give any explanation of the relation of hepatic function to carbohydrate metabolism as a whole. He claims the theory does not explain the observed correlations of liver functions with peripheral tissue utilization of sugar. Himsworth feels the theory "regards the blood sugar level as an expression of activity of the liver and this activity as being determined not by the needs of the tissues for carbohydrate but by the particular state of the liver at any time." As an example of inadequacy of the theory he cites the effect of starvation. In this state the blood sugar tolerance curve is elevated to high levels and with this heightened blood sugar there is normally an increased peripheral tissue utilization of sugar. However, after starvation he claims there is a great diminution in the normal effect of glucose in increasing the oxidation of carbohydrate and with an impairment of carbohydrate utilization by the peripheral tissues.

Commenting on Soskin's theory that "hypophysial extracts lower the threshold at which the liver secretes sugar into the blood," Himsworth claims it does not explain why the extracts simultaneously inhibit insulin action in the peripheral tissues. However, Himsworth advances a working hypothesis based on the findings of certain investigators that tissue sugar utilization increases proportionally with the height of the blood sugar level, and the height of the blood sugar is regarded, "metaphorically, as a head of pressure of sugar in the blood." In health he claims this head of pressure being

recognized as within normal limits ensures that the normal utilization of carbohydrates by the tissues proceeds at an adequate rate. If tissue utilization of carbohydrate is impaired either by insulin insufficiency or impairment of action, there occurs a compensation through an appropriate increase in the head of pressure of sugar in the blood, thereby maintaining a relatively constant rate of utilization of tissue sugar. He is of the opinion that hyperglycemia of diabetes, "is a controlled and compensatory phenomenon" with the object of facilitating glucose utilization by the tissues. The hyperglycemia, he feels, is caused by the increased activity of the liver with the anterior pituitary gland playing an important factor in this activity. He attributes diminished tissue utilization of glucose to either insulin deficiency or insensitivity with hypersecretion of anterior pituitary playing an important part in causing insulin insensitivity.

Diabetic Meal Tolerance

We decided to extend the same studies of the effects of the meal upon the normal and medical (non-diabetic) patients to a few of the diabetics with various complications — gangrene, blindness, hypertensive cardiovascular disease, pulmonary tuberculosis, etc. (TABLE III).

We observed a marked increase of the average blood sugar levels during the absorption of the meal as compared with fasting. The maximum average increase was noted at the end of the first hour post-prandially, a difference of 132 mg., as compared with the average fasting. However, the average blood sugar level was maintained at a high level — above 300 mg. — for the first 3 hours post-prandial, whereas at the end of 1½ hours a gradual descent of the blood sugar from 375.5 mg. to 344.1 mg. became apparent which Graph I graphically illustrates. A decided descent to 285.2 mg. of the average blood sugar became very evident at the end of the 4th hour (post-prandial) although the sugar concentration was still higher than the average fasting. Thus, throughout the average 4 hour post-prandial the blood sugar level remained higher than the average fasting.

In some of the individual cases we noted a marked elevation of the blood sugar post-prandially as compared with the fasting. Thus in Case No. 3, we found a fasting blood sugar of 260 mg., whereas 1 hour post-prandial it was 592 mg., a difference of 332 mg. It is thus apparent from the above observations that the disturbance in metabolizing the food in the diabetic becomes most marked within 1 to 3 hours after meals.

In our past studies with plain insulin as well as in our more recent observations as shown in Table No. IV, the average blood sugar level was lowered within ¾ hour after the insulin is injected, with the maximum reduction in the blood sugar between 2¾ to 3¾ hours. Apparently the hypoglycemic action of the plain insulin was also extended 1 hour after lunch. From our observations the action of plain insulin was rapid, taking effect within ¾ hour and extended over 5 hours.

Blood sugar studies of the meal tolerance were undertaken with protamine zinc insulin but extended

TABLE III

Diabetics Meal Tolerance

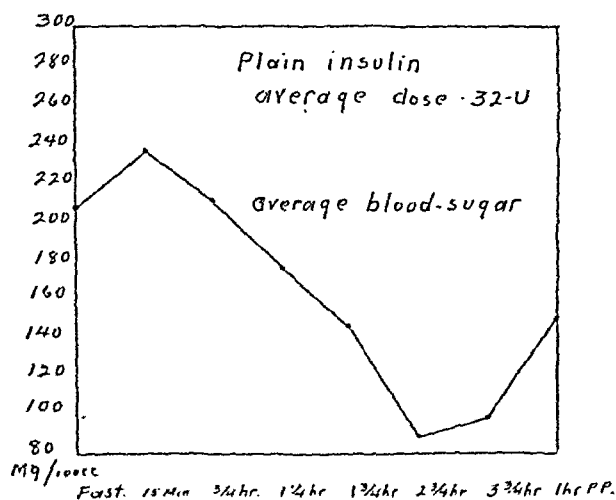
Initial of Patient	Age of Patient	Weight	Sex	Fast.	Blood Sugar Level mg/100 cc. After Breakfast						Comments
					1/2 hour	1 hour	1 1/2 hours	2 hours	3 hours	4 hours	
J.W.	63	136	M	192	284	254	246	234	206	206	Diabetes 2 years duration; previous treatment with "pancreas capsule"
D.H.	48	199	F	218	312	324	298	284	250	224	Diabetes newly discovered; symptoms of 7 months duration; chr. right otitis media, acute bronchitis
R.P.	39	125	F	260	392	592	464	360	322	300	Diabetes for 1 year; bilateral. Fibro-ulcerative pulmonary T. B.
M.D.	62	126	F	290	412	432	412	400	360	350	Diabetes discovered a year ago; ulcer of right leg; hypertensive C.V. disease
M.V.	59	158	F	176	234	258	256	244	193	170	Diabetes discovered 7 years ago; no previous treatment. Hypertensive C.V. disease; acute gastric upset, cause unknown
A.S.	72	136	F	248	312	366	420	378	370	352	Diabetes discovered 5 years ago; never took insulin; blindness due to hypertensive retinopathy; perforating ulcer of the left large toe
A.F.	60	127	F	264	392	424	400	364	356	332	Diabetes newly discovered; gangrene left foot (performed mid-thigh amputation); hypertensive C.V. disease
M.J.	36	91	F	256	464	464	448	400	300	264	Hypertensive C.V. disease
M.H.	55	128	F	270	344	362	392	352	350	350	Diabetic gangrene or right foot, mid-thigh amputation performed; diabetes 2 years
L.J.	78	105	F	310	390	400	416	370	332	314	Diabetes 3 months, according to symptoms
E.S.	59	185	F	228	336	375	379	400	285	276	Hypertensive C.V. disease; arteriosclerosis retinopathy
Average	54.6	137.8		246.5	352	386.4	375.5	344.1	302.1	285.2	

TABLE IV
Plain Insulin

Blood Sugar Level After Breakfast

Patient	Sex	Age	B-Sugar Fast.	Insulin dose	15-20 min.	1/4 hour	1 1/4 hours	1 3/4 hours	2 1/2 hours	3 1/2 hours	Lunch—1 hour after
1	F	62	260	16	243	260	240	207	157	134	134
2	M	60	217	40	286	203	183	166	85	60	183
3	M	59	224	50	260	235	207	150	60	50	134
4	F	34	125	20	157	150	80	63	50	50	150
Average			206.5	31.5	236.5	212	177.5	146.2	88	73.5	150.25

Graph. 2



over a longer interval as shown in Table No. V. They revealed in patient (2) an initial drop of the blood-sugar at 4:30 P. M., 8 1/2 hours after the insulin injection with effects still continuing at 7 A. M., a duration of 23 hours. Even after an interval of 23 hours the effects of protamine zinc insulin were apparent as noted by a lowest blood sugar level of 175 mg. In spite of 5 feedings (breakfast, lunch, supper, late evening and breakfast the next day) the effects of the protamine zinc were still persistent 2 hours after breakfast at 10 A. M. and also 3 1/2 hours after breakfast, at 11:30 A. M., as revealed by the blood sugar levels of 201 mg. and 264 mg. respectively 26 and 27 1/2 hours after the protamine zinc insulin injection. These blood sugar levels were lower than the fasting level of 280 mg. at the onset of the present studies, as shown in Graph No. 3.

Protamine Zinc Insulin Therapy

The above studies reveal the marked difference between the protamine and plain insulin rate of action which was first realized by one of us soon after the development and general use of protamine zinc insulin (47). It then became apparent that this new insulin compound, protamine zinc insulin, though possessing certain advantages over the unmodified or regular insulin, had marked limitations as well as marked disadvantages.

Our subsequent studies of 1,093 diabetics revealed that in 50% of the cases it was necessary to combine plain insulin with protamine zinc insulin so as to help reduce the increased blood sugar caused by the high carbohydrate diets. This group of 50% comprised

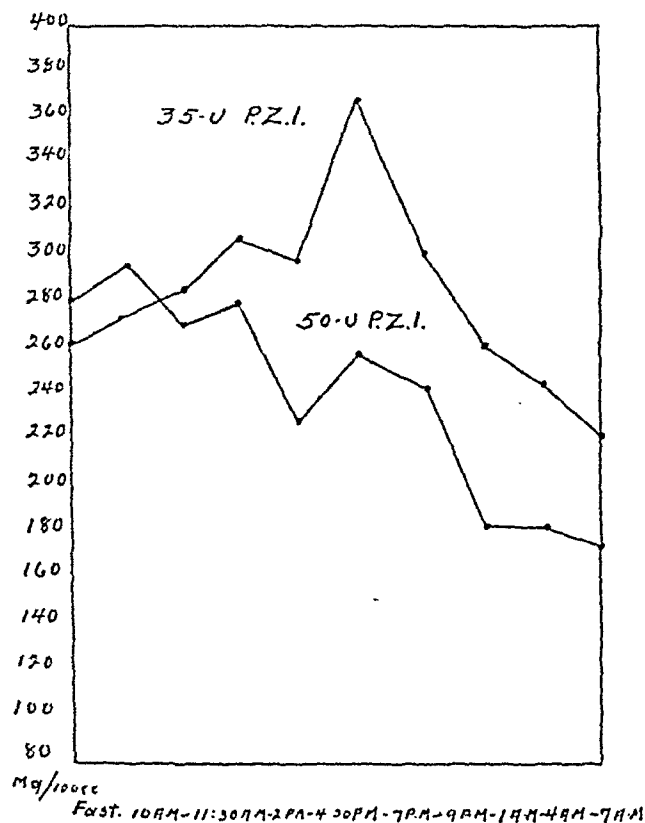
TABLE V

Protamine Zinc Insulin

Blood Sugar Level mg/100
Breakfast Lunch Supper

Name of Patient	Sex	Age	B-sugar Fast.	Protamine Insulin dose	10 A.M.	11:30 A.M.	2 P.M.	4:30 P.M.	7 P.M.	9 P.M.	1 A.M.	4 A.M.	7 A.M.	Complications
H.P.	F	65	261	35	275	285	308	300	369	300	261	247	222	Diabetic ulcer right foot
M.L.	F	50	280	50	297	272	280	229	257	243	184	184	175	Hypertension C.V. disease

Graph 3



However, there were patients, 16% of the cases, whose slight fluctuation of the blood sugar was "apparently controlled" by one injection of protamine. The dose of the insulin varied from 10 units to 80 units. The age of the patients ranged from 28 years to 85 years. Although no attempt was made to change to plain insulin, a few of the patients in this group could have been controlled by plain insulin.

In the younger group, however, it was not possible in most instances to control adequately the blood sugar level without combining the protamine zinc with plain insulin. This group appeared to be more dangerous because the physician in prescribing one injection of the protamine insulin was often satisfied by a fasting blood sugar within the so-called "normal range" of 140 mg. It was not uncommon to observe protamine zinc insulin patients with a blood sugar of 140 mg. who looked well with no suspicious hypoglycemic symptoms but who developed acute insulin coma or shock in early morning hours, or at intervals when the shock is least expected.

The same hypoglycemia reactions occurred when protamine zinc insulin was combined with plain insulin.

Globin Insulin

Since the introduction of protamine zinc insulin another, a more recent, insulin compound with prolonged action called globin insulin with zinc usually referred to as globin insulin has been prepared for the treatment of diabetes (48). The compound is a pale amber, almost colorless, aqueous solution containing 40 or 80 units of insulin per cc., 3.8 mgm. of purified globin derived from the hemoglobin of beef blood, and 0.3 mgm. of zinc as zinc chloride per 100 units of insulin. The pH of this insulin preparation is about 3.7, an acidity which helps to maintain the preparation sterile and stable. Upon each package containing the globin insulin is an expiration date after which it should not be used, although no change in potency or duration of action has been noted after storage in refrigeration for 2 years.

Laboratory observations (48) of globin insulin have revealed that the hypoglycemic effect after injection was longer than the standard or the plain insulin and not as long as the protamine zinc insulin. However the hypoglycemic action is more rapid in its onset than protamine zinc insulin and becomes intense in a few hours, after which it gradually wanes (49).

Clinically the onset of the hypoglycemic action of globin insulin has been shown by various investigators to take place within 2 hours after it has been given

those patients who required plain insulin with protamine zinc insulin for one meal, either breakfast or supper, and those who in addition to these combined insulins required plain insulin at another meal, i. e., either for breakfast or supper. In none of the patients was it necessary after the stabilization or "control" of their diabetes to give insulin for lunch (mid-day meal). The age of the patients varied from 6 years of age to 84 years; total daily dose of both insulins varied from 24 to 200 units. In some instances the dose was higher, even totalling 1350 units for a few weeks in one case.

However, in neither groups comprising the 50% were the patients completely free from hypoglycemic symptoms. We observed that a few patients developed a peculiar dread of protamine zinc insulin reaction. They often dreaded sleeping alone because of the frequency of early morning reactions. It was not uncommon for patients to awaken with tingling sensations around the mouth or on the fingers, or in a mental stupor to be succeeded by a profound insulin coma.

subcutaneously (50, 51) and lasting for a period of from 12 to 16 hours (52), in some cases to 24 hours (53). Some investigators (53) revealed a varied duration with the dose and severity of the diabetes — larger dose will generally cause a more prolonged action, whereas a smaller dose a less prolonged action. Eight time-activity curves-doses 10 to 80 units showed that the duration was in general 14 to more than 24 hours with an average duration of 18 to 19 hours (53). Although the initial onset of action was within 1 hour after its injection it was slow for the first 3 to 5 hours.

It appears that the studies of the various clinical investigators on the relationship of the action of globin insulin to the absorption of the carbohydrate of the meal has been to re-arrange the daily distribution of the carbohydrate allowance so as to meet the maximum hypoglycemia effect of the insulin. Since the maximum hypoglycemia action as observed by clinical investiga-

This long interval before breakfast has also been generally advocated for protamine zinc insulin (57).

It has also been shown through clinical observation that globin insulin rarely causes local skin reaction as compared with protamine zinc insulin or even generalized urticaria or constitutional reactions. Intradermal tests using the substance protamine showed that skin reactions were 24 times more frequent than with the substance globin (58).

Experimental Observations

As a result of the findings of various clinical investigators upon the duration of action of globin insulin, we decided to make a 24 hour study of its effect upon the blood sugar curve of a group of known diabetics suffering from various complications who were upon high carbohydrate diets ranging from 120 to 200 grams for the total day divided equally into the three meals

TABLE VI
Globin Insulin with Zinc

Blood Sugar Level mg/100 cc.

Name	Age	Sex	B-sugar Fasting	Insulin dose	10 A.M.	11:30 A.M.	2 P.M.	4:30 P.M.	7 P.M.	9 P.M.	1 A.M.	4 A.M.	7 A.M.	Complications
E.M.	45	F	215	20	326	318	199	106	182	182	225	199	194	Carbuncle on back
S.R.	57	F	369	40	432	444	346	183	225	166	240	222	261	
M.D.	27	F	193	45	289	247	228	188	210	152	228	172	144	Sinistisus
M.L.	47	F	358	35	389	276	229	263	248	210	250	162	161	Infected left foot
M.K.	64	F	87	35	250	140	157	122	166	135	67	45	58	Ulcer of left leg
L.G.	67	F	102	30	185	148	177	126	126	126	140	140	162	Carbuncle left arm
Average			221	34.1	306	262.1	222.6	166.3	193.3	161.8	192.1	156.6	164	

tion takes place between 6 to 10 hours, it was found by Martin and associates (53) to be most practical to re-arrange the daily carbohydrate allowance by giving 1/6 carbohydrate at breakfast and 1/3 at lunch; 1/6 at 3 P. M. and 1/3 at dinner with a bedtime feeding. Protas (50) advises carbohydrate ratio 1/5, 2/5, and 2/5 respectively for breakfast, lunch and dinner, with 5 to 10% allowance in afternoon to offset any hypoglycemic action. Marks (54) speaks of a more normal daily distribution of carbohydrate. Instead of four feedings, he feels only three are required. Greenhouse's (55) diet routine for globin insulin is similar to that of protamine zinc insulin with the exception of giving extra feeding in the afternoon for globin insulin patients instead of evening feeding as for the protamine zinc insulin patients. He divided his total daily carbohydrate allowance as 2/10 for breakfast, 3/10 for lunch, 4/10 for supper and 1/10 for extra feeding. Andrews and his associates (56) advocate 2/10 of the daily carbohydrate allowance for breakfast, 4/10 for noon meal, 1/10 for four o'clock lunch, and 3/10 for evening meal with the protein and fat divided so as to meet the individual routine. Advocates of globin insulin claim the insulin action is extended throughout the three meal periods of the day when its action is most needed.

Advocates of globin insulin have claimed better results by administering it subcutaneously about one hour (52), others (51), 30 to 45 minutes before breakfast.

(breakfast, lunch, supper). The age variations were from 16 to 67 years. Single doses of globin insulin given varied from 25 units to 40 units. These patients had no previous insulin therapy and the globin insulin was administered upon admission to the service.

In preference to administering the single dose of globin insulin before the meal, in our studies it was given immediately after breakfast. The patients ate their regular prescribed meals (breakfast, lunch, supper), while the blood specimens were obtained at the designated intervals throughout the 24 hour study.

Blood sample for sugar estimation was taken at 7 A. M. followed by the prescribed breakfast and the insulin dose. Blood samples were thereafter obtained at 10 A. M. and just before the prescribed lunch at 11:30 A. M., at 2 P. M., just before supper 4:30 P. M., and finally at 7 P. M., 9 P. M., 1 A. M., 4 A. M. and 7 A. M., making a total of ten (10) blood sugar estimations.

The effect of the average globin insulin dose could not be accurately evaluated in the average post-prandial rise of the blood sugar at 10 A. M. caused by the breakfast. The effects of globin insulin began to become apparent on the average blood sugar level at 11:30 A. M. — 3½ hours after breakfast and just before lunch. At this time there was a lower blood sugar than the fasting level. The globin insulin hypoglycemic effect continued to 4 A. M. (20 hours after its injection)

as shown by the gradual drop of the average blood sugar level. The blood sugar level then began to rise as shown by the slight increase at 7 A. M. over the 4 A. M. level. It became apparent that the action of globin insulin was effective when most desired — during meal time (lunch-supper) with a "tailing" effect, after midnight.

In the individual instances when the globin insulin (35 units) was given immediately after breakfast — 8 A. M. as in Case No. 4, we observed a drop of the blood sugar $3\frac{1}{2}$ hours after globin injection, at 11:30 A. M., and which continued for 23 hours as shown by the blood sugar level of 161 mg. at 7 A. M. This latter observation was also very evident in Case No. 3: when a larger dose of globin insulin at 8 A. M. (45 units) caused a drop of the blood sugar $3\frac{1}{2}$ hours later and also continued for 23 hours as revealed by the blood sugar level of 148 mg. at 7 A. M. In Case No. 2, the blood sugar level continued to drop slowly reaching the lowest level at 166 mg., 13 hours after its injection at 9 P. M.

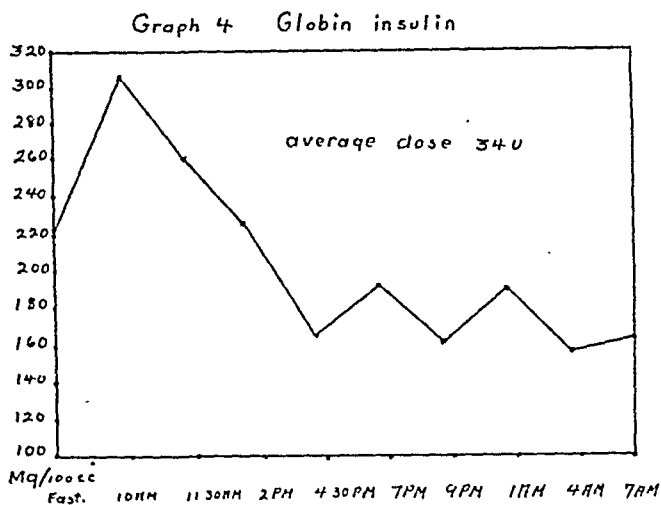
In Case No. 1 when 20 units of globin insulin were given at 8 A. M., a drop of the blood sugar occurred $3\frac{1}{2}$ hours later, at 11:30 A. M., with the maximum effect obtained $8\frac{1}{2}$ hours after the insulin injection, at 4:30 P. M., as revealed by the blood sugar level of 106 mg. The insulin effects mildly continued to 7 A. M., length of insulin action being 23 hours. In Case No. 5, globin insulin action became apparent $3\frac{1}{2}$ hours after its administration, with the maximum effect obtained 20 hours after the insulin injection as shown by the blood sugar level of 45 mg. at 4 A. M., after which a rise of the blood sugar level occurred at 7 A. M. to 58 mg. (23 hours after insulin injection). In Case No. 6, initial globin insulin action was observed $3\frac{1}{2}$ hours after its injection, 11:30 A. M.; whereas the maximum effect was $8\frac{1}{2}$ hours after its injection, at 4:30 P. M., and continued until 9 P. M. (13 hours after its injection). This insulin action began to wane at 1 A. M. (17 hours after insulin injection) as shown by the blood sugar rise of 140 mg. at 7 A. M. to 162 mg.

Thus we observed in most instances globin insulin action within 2 to $3\frac{1}{2}$ hours lasting 20 hours after its administration, in some cases 23 hours with maximum effect in most instances in $8\frac{1}{2}$ hours. The duration of action of globin insulin generally depended upon the dose of insulin — the larger the dose the longer the interval of the maximum effect and duration of action.

Clinical Application

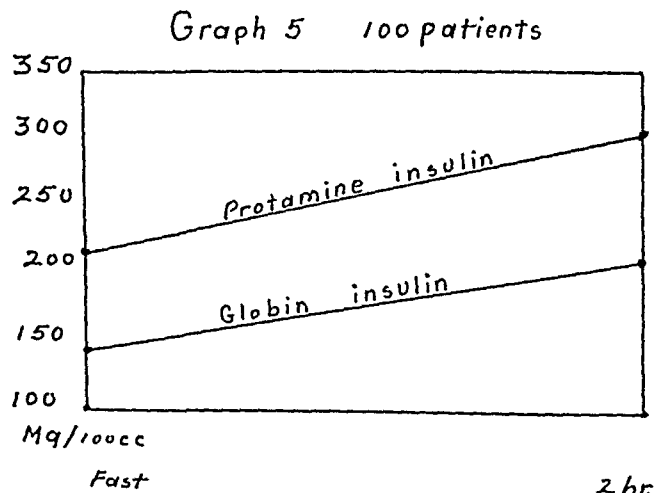
Upon the above facts we decided to make a comparative study of protamine zinc insulin and globin insulin in a group of patients who had been upon protamine zinc insulin alone and in those upon protamine and plain insulin combined for a variable period of a few months to years and who suffered from cardiovascular complications as well as infectious disorders. This group consisted of 100 diabetic patients with age variation from 12 to 73 years with an average age of 55 years. Both groups of insulin (protamine and plain)

patients upon admission to the metabolic service had an average fasting blood sugar level of 214.2 mg. and



an average post-prandial (2 hours after breakfast) 300.3 mg. In spite of these somewhat elevated blood sugar levels many of the patients suffered from mild to severe signs and symptoms of hypoglycemia reactions in late afternoon, early evening or morning hours as well as late morning, and frequently just before and during breakfast time. This group of 100 patients with protamine alone or combined with plain insulin were transferred to globin insulin alone or in conjunction with plain insulin. The average fasting blood sugar level of the globin insulin patients was 144.6 mg., and the average post-prandial (2 hours after breakfast) was 211.2 mg. upon discharge from the hospital.

The globin insulin patients were also subject to hypoglycemia reactions. These reactions were generally symptomatic in character as compared with the protamine insulin patients whose hypoglycemia reactions were not infrequently asymptomatic. However, reactions with globin insulin usually occurred in late afternoon when the blood sugar level (1 to 3 hours) after breakfast was maintained below 150 mg. per 100 cc. When the post-prandial blood sugar ranged between 170 and 220 mg., these afternoon reactions became less frequent.



Blood sugar examinations were made at 4 P. M. of another group of patients (total 31) who were given globin insulin alone or combined with plain insulin immediately after breakfast. The average blood sugar level at the 4 P. M. interval was 204 mg. per 100 cc.

Summary of Observations

In spite of the methods of determining the state of the diabetic's carbohydrate metabolism — fractional or 24 hour urine for examination of sugar content or upon the blood sugar of the patient before a meal as guides for the correction of the disturbed metabolism by diet and insulin, protamine zinc and plain, our clinical observations and the findings of other investigators as revealed by the literature confirm the increased incidence of degenerative vascular complications of diabetes as well as its resultant invalidism and mortality rate.

The effect of a higher carbohydrate meal (breakfast: 32 grams of protein, 64 grams of fat and 95.6 grams of carbohydrate, a total of 1086.4 calories) upon the blood sugar levels of normal persons and medical (non-diabetic) patients with various pathological disturbances is to produce a lower average blood sugar level post-prandially after the first $\frac{1}{2}$ hour and after the first hour respectively during the 4 hour interval after breakfast than their average fasting blood sugars.

In spite of the pathological disorders of the medical (non-diabetic) patients, the blood sugar results revealed that their carbohydrate metabolism was not generally affected and was somewhat similar to that of normal persons. Most of the medical patients because of physical disability were confined to bed. It is very significant that they revealed practically no disturbances of the blood sugar level 1 hour following the absorption of the higher carbohydrate diet.

Experimental studies indicate that the blood sugar is derived from liver glycogen, the source of which in turn is not only carbohydrate material, but also non-carbohydrate food (protein, fatty acid and small molecules which may arise in the course of metabolism from various sources).

The mode of control of the blood sugar level is still a controversial problem. Some investigators are of the opinion that the blood sugar level is under the influence of hormone equilibrium with the pancreas playing a fundamental role through its insulin secretion; others claim a homeostatic regulation of the blood sugar by the liver in the presence of sufficient insulin and not necessarily extra secretion. These latter investigators claim the normal liver glycogen function to be under the influence of proper endocrine balance which determines normal carbohydrate tolerance curve. There are other investigators who hold the belief that the extra insulin or increased insulin secretion of the pancreas caused by the administration of dextrose is responsible for the normal dextrose tolerance. Himsworth takes exception to Soskin's theory of the homeostatic function of the liver and advances a working hypothesis that tissue sugar utilization increases proportionally with the height of the blood sugar level, and the height

of the blood sugar is regarded, "metaphorically, as a head of pressure of sugar in the blood." Normally he claims this head of pressure ensures the normal utilization of carbohydrate by the tissues to proceed at an adequate rate.

The effects of the higher carbohydrate meal upon the blood sugar levels of diabetics revealed a marked elevation post-prandially as compared with the fasting blood sugar level — a difference which is compatible with the disease, a disturbance in metabolizing the food.

Our observations in a group of diabetic patients upon a higher carbohydrate diet revealed that action of plain insulin is rapid, taking effect within $\frac{3}{4}$ hour and extended over a five hour period.

The hypoglycemic effect of protamine zinc insulin became apparent $6\frac{1}{2}$ hours after its administration and continued for $27\frac{1}{2}$ hours as revealed by the lower blood sugar level than the blood sugar before the meal at the onset of our studies.

A newer insulin compound, globin insulin with zinc, has been introduced into diabetic therapy. Experience has revealed its action to be more rapid in onset than protamine zinc insulin and slower than the plain insulin but with a longer duration than plain insulin and a shorter interval of action than protamine zinc insulin. The literature as well as our observations have revealed that globin insulin provokes fewer allergic reactions than protamine zinc insulin.

Twenty-four hour studies with globin insulin upon patients on higher carbohydrate diets divided equally into three meals, revealed in the average patient an initial drop of the blood sugar within $3\frac{1}{2}$ hours after its injection, a maximum effect within $8\frac{1}{2}$ hours, and hypoglycemic action continuing 20 hours.

Clinical comparison of protamine zinc insulin with globin insulin was made as to their effects upon the blood sugar of a group of 100 patients.

Interpretations of Our Observations

The physician who observes the increased incidence of degenerative vascular complications and higher mortality rate, ponders as to what is the ideal diabetic therapy. Has it been proved that hyperglycemia or glycosuria is detrimental to the body metabolism or is inductive of premature degenerative vascular lesions? Is symptomatic or asymptomatic hypoglycemia occurring at infrequent intervals with variable duration as unavoidably induced by physicians when administering the slower acting insulins, as they strive for urine sugar-free or normal (non-diabetic) blood sugar level harmful?

In our studies with normal and medical (non-diabetic) patients we have found that the blood sugar levels after meals, in the 4 hour period as judged in 30 and 60 minute intervals were generally slightly lower than the blood sugar level before the meal. The medical patients who were confined to bed because of pathological disorders revealed no disturbances in their carbohydrate tolerance after the first hour following the higher carbohydrate meals. The glucose tolerance examination was ignored because we are in accord with

Soskin who claims it is merely an artificial strain upon the regulating mechanism in a quantitative form. In the diabetic patients, however, the disturbance in metabolizing the meal became very evident by the higher blood sugar levels post-prandially than the fasting (blood sugar level before the meal).

Thus it became apparent that in the normal and in the medical patients (non-diabetic) the blood sugar levels after meal (30 to 60 minute intervals) revealed little change, whereas in the diabetic it became markedly elevated after a meal as compared with the blood sugar before the meal. It was obvious that if a single examination, fasting blood sugar as commonly practiced by a majority of the physicians, was the sole laboratory criterion for the determination of the existence of diabetes many diabetics would escape detection. We observed many diabetics with normal or even below-normal fasting blood sugar level whereas, following a meal, the blood sugar became markedly elevated. This observation became very evident upon admission of 329 diabetics with various complications on protamine zinc and plain insulin combined or protamine zinc insulin alone. In this group we observed 104 diabetic patients with apparently normal (non-diabetic) fasting blood sugar level who had an average blood sugar level of 129.8 mg. before breakfast and an average 2 hour post-prandial of 230 mg.

In stabilizing (diet, insulin, etc.) our diabetic patients we aim to bring the post-prandial blood sugar level (1 to 3 hours, generally 2 hours after meals) with the level most compatible for the individual patient. We have observed that many patients, even though their diabetes was controlled, free from diabetic symptoms or signs as thirst, hunger, loss of weight, polyuria, urine negative for acetone, with a variable degree of hyperglycemia and glycosuria — felt better mentally and physically when we reduced the post-prandial blood sugar level within the range most compatible for the patient's physical condition irrespective of the degree of glycosuria. Several factors were considered to determine the compatible post-prandial blood sugar level: condition of cardiovascular system, existing complications, age of the patient, and symptomatology. A post-prandial blood sugar level 170 to 220 mg. was generally considered compatible. These blood sugar values were based upon the studies of 1538 diabetics with age variations from 28 months to 87 years. These blood sugar levels are also subject to variation. Thus it is not uncommon to observe diabetes complicated with coronary disease as in a patient aged 80 years who felt better and free from diabetic signs and symptoms with a post-prandial blood sugar of 300 mg. However, when the blood sugar was reduced to a lower level, 180 to 200 mg., the patient had subjective symptoms — pressure sensation across chest anteriorly, slight dyspnea and marked weakness, etc.

It is also apparent from our studies that not infrequently the greater the damage to the vascular system, the higher the blood sugar level. We are in agreement with Himsworth who is of the opinion that hypergly-

TABLE VII

Blood Sugar Levels mg/100 cc.

104 Cases Before meal (fasting) and 2 hours after meal (post-prandial)

Fast.	2 hrs.	Fast.	2 hrs.	Fast.	2 hrs.	Fast.	2 hrs.
190	250	122	244	112	193	116	200
123	216	118	192	115	183	188	232
60	174	91	186	113	183	150	190
136	192	126	244	135	195	113	238
114	226	112	193	114	170	139	236
122	192	104	250	184	340	162	232
130	204	157	300	117	200	82	158
160	198	153	248	157	183	112	210
157	290	98	204	153	240	150	300
178	160	122	210	116	192	182	376
102	224	98	204	118	284	173	310
103	183	176	222	129	190	96	230
120	230	122	210	131	262	107	220
127	190	150	240	100	204	123	196
77	224	94	270	140	210	105	360
102	220	170	270	135	188	120	206
140	195	104	250	55	264	60	270
157	250	153	197	122	210	66	188
74	169	157	300	91	186	118	192
176	260	153	248	166	193	142	200
166	224	166	220	163	230	122	244
170	272	154	280	178	266	130	256
169	308	93	240	171	220	130	210
100	204	158	192	56	172	120	230
131	262	126	244	180	236	127	190
135	195	166	280	131	180	102	224

cemia of diabetes, "is a controlled and compensatory phenomenon with an object of facilitating glucose utilization by the tissues."

However, many physicians still adhere to the idea that a diabetic to be considered controlled or stabilized must have a fasting blood sugar level of that of a normal person, 80 to 120 mg. This method of blood sugar control by diet, and insulin if necessary, often invites serious reaction or even fatal results. An instance is that of a diabetic woman aged 72 years who had a blood sugar level of 340 mg. Though she was diabetic symptom-free, her physician thought it advisable to administer a large dose of insulin because of the elevated blood sugar level. Within a short period of a few hours the patient was admitted to our metabolic service in profound insulin coma and left sided hemiplegia. She died within 3 days of her admission.

Arteriosclerosis

Since the introduction of the slow-acting insulins in diabetic therapy, there has existed much confusion as to the method of achieving "adequate" diabetic care for the prevention of premature arteriosclerosis. Many physicians believe that the continued action of the protamine zinc insulin as revealed by the 24 hour or fractional urines for sugar or by its apparent ability to maintain a blood sugar level equivalent to the normal (non-diabetic) person's will help to delay the onset of premature arteriosclerosis. Since a review of the literature reveals the etiology of arteriosclerosis to be unknown, the above assumption lacks clinical and laboratory proof.

Lawrence's (59) observations disagree with the opinion that negative urine or better control of the diabetes — blood sugar level approaching the normal — prevents onset of premature arteriosclerosis. His stud-

ies of 43 diabetic children treated for 10 or more years with insulin, many on low carbohydrate diets, and most of them with their diabetes not controlled well, revealed no evidence of vascular disease, with one exception. He attributes the pituitary as a responsible factor for occlusive arterial changes, confined mostly to the middle aged and elderly diabetic patients usually having mild diabetes and no marked hypercholesteremia. Wilder and Wilbur (60) in their discussion of the relationship of diabetes and arteriosclerosis claim that the metabolic disturbance is not confined to the metabolism of lipoids. They feel that "hyperglycemia, ketosis or the frequent occurrence of infections can just as well be held responsible for the arteriosclerosis in the disease. Periodic dehydration, the frequency with which diets are inadequate in certain nutritional factors, such as some of the vitamins and salts and the possibility that patients with diabetes require more than a normal supply of certain vitamins, are other possible explanations. Nor is it clear that the severity of the arteriosclerotic changes in persons with diabetes parallels the degree of elevation of the lipoids in the blood." He mentions Hunt's (61) observations, who found patients with lowest average cholesterol levels having the most advanced arteriosclerosis. Page (62) is of the opinion that arteriosclerosis is insidious, although insidious is a relative term. His reason is based upon the poor methods for determining arteriosclerosis early. What may now be called insidious, "may later prove to be a more fulminant process." Page expresses belief that arteriosclerosis can be delayed "if it is being accentuated by the occurrence of hypertension by abolishing the hypertension . . . Even that is not proved." As to the delay of the onset of premature arteriosclerosis: "I think it remains to be proved that arteriosclerosis can be decelerated by adequate insulin treatment in diabetes. Again, such work is seriously handicapped by inability to detect anything but extreme changes in the sclerosis of the vessel walls."

Tolstoi's (63) experience with protamine zinc insulin over a five year period concludes that the evidence from the assumption that complications such as vascular degenerative lesions are attributable to hyperglycemia and glycosuria, are inferential and inconclusive. Wagener (64) expresses the belief based upon his studies that no form of diabetic control now employed has been shown to prevent the development of retinitis or its steady progression when once it has been well established. Tooke and Nicholls (65) claim that diabetic retinitis is not caused by diacetic acid, acetone or by hyperglycemia. Despite treatment they are of the opinion that the changes tend to be progressive, and the prognosis of diabetic retinopathy they feel while worse than that of a simple arteriosclerotic condition, is not good in the presence of arteriosclerosis or hypertension as regards vision or expectancy of life.

Hueper (66) is of the opinion that the onset of "atherosclerosis" in man is as a rule insidious . . . "Arteriosclerosis . . . may have a relatively rapid development, when it is caused by disturbances of calcium

metabolism or by severe and frequent attacks of hypertonic or hypotonic reactions."

Daley and his associates (67) are of the opinion that the association of hypertension with diabetes accentuates the development of atherosclerotic lesions. They observed the frequency in severe retinal lesions of advanced sclerotic changes in the aorta and coronary arteries at necropsy. Schroeder and Steele (68) describe the frequent association of generalized arteriosclerosis and "essential" hypertension with the possible thought of some intimate relationships between them. Newburger and Peters' (69) clinical and post mortem observations of a group of cases with similar features and a characteristic lesion, warrant the grouping of them together as a distinctive disease picture, intercapillary glomerulosclerosis, with constant features such as diabetes, albuminuria, hypertension and retinal vascular changes. They are of the opinion that the pathogenesis of this condition "depends on severe and extensive arterial and arteriolar degeneration, associated with, and perhaps resulting in, diabetes mellitus, hypertension and renal damage."

Veal (70) interprets arteriosclerosis as a systemic disease which implies a generalized degeneration of the whole vascular tree, gangrene being a local manifestation or warning of the generalized vascular deficiency. He is of the opinion that the vital organs, the brain, myocardium and the kidneys, are also impaired by the circulatory impairment and in a state which he terms "locus minoris resistentiae." The margin of safety for the non-gangrenous parts of the vascular system, although compensating, is slight, and undue strain or stress may precipitate failure of the entire system. Thus he claims "arteriosclerosis is a progressive disease . . . as the patient grows older, progressively greater destruction of the vascular bed occurs . . . greater involvement of the vital organs — the heart, the kidneys, and the brain, as well as the peripheral blood vessels."

Roab (71) is of the opinion that the progress of arteriosclerotic vascular changes is greatly enhanced by adrenal activity. Other investigators (72, 73) are of the opinion that a disturbance of the cholesterol metabolism plays an important part in the etiology of arteriosclerosis. This latter view of disturbed cholesterol metabolism is still controversial (74).

It becomes apparent that physicians in attempting to achieve "better" control of diabetes with the slow acting insulin — urine free from sugar, blood sugar level approaching the normal (non-diabetic) with the hope of warding off or delaying the onset of a premature arteriosclerosis have created, in the opinion of the present writers, a condition, hypoglycemia, which may have multiple, serious end-results.

When we observed pronounced and somewhat prolonged hypoglycemia at not infrequent intervals in patients upon the slow acting insulin, the thought came to us of its possible production of vascular injury or of its being a contributing factor in hastening vascular degeneration as based upon the anoxemia theory. This thought postulated upon the fact that during insulin

hypoglycemia the brain is affected in the same way as when suffering an oxygen deficiency. Hueper seems to believe the possibility that a "severe and persistent hypoglycemia may interfere with the nutrition of the vascular walls," even though he has not evaluated the existing literature on hypoglycemia. Therefore he is not able "to say whether or not hypoglycemia actually has such an effect."

Page (62) expresses doubt "that insulin hypoglycemia, unless it were very profound and prolonged, would interfere sufficiently with the oxidative metabolism of the vascular wall to bring about vascular degeneration in diabetes." It is obvious from our observations that very profound and prolonged hypoglycemia is seen with sufficient frequency in patients upon the slow acting insulin to warrant suspicion as to its possibility of precipitating a state of hypoxia which "may contribute" in premature vascular degeneration.

CONCLUSION

1. "Adequate diabetic control" as based upon fractional or 24 hour urine for examination of sugar content or upon the blood sugar of the patient before a meal has not decreased the incidence of vascular degenerative complications.

2. Blood sugar levels of a normal person after an average breakfast — (four hours period: 30 minute intervals for the first two hours, and the third and fourth hour of the remaining interval) reveals little difference as compared with the fasting blood sugar. However, the post-prandial blood sugar levels were slightly lower than the fasting after the first 30 minutes.

(a) In medical patients (non-diabetic), with the exception of the first hour after the meal, the blood sugar levels approached the normal person's.

(b) The blood sugar levels of the diabetic after the meal became markedly elevated throughout the entire post-prandial interval as compared with the fasting.

3. Fasting blood sugar is not a complete index of the diabetic's metabolic power for carbohydrate, and

may often be misleading when it is the sole laboratory guide of the diabetic's progress.

(a) One to three hours, generally two hours after an adequate normal meal is the interval of choice for determining the diabetic's metabolizing power for food.

4. To control or "stabilize" the blood sugar level of a diabetic does not necessitate its reduction to the same level as a normal person's — as is the general procedure of physicians.

5. The general belief among many physicians that uncontrolled hyperglycemia or glycosuria is inductive of premature vascular degeneration in diabetes lacks proof.

6. Hyperglycemia of diabetes is a "controlled and compensatory phenomenon with the object of facilitating glucose utilization by the tissues."

7. Compatible blood sugar level for the diabetic, though generally higher than that of the normal person, should depend upon the condition of the cardiovascular system, age of patient, and existing complications. It is the level most compatible to his well-being, generally 170-220 mg., post-prandial, that should be maintained.

8. Since the introduction of the slow-acting insulin in diabetic therapy, physicians in attempting to reduce the hyperglycemia to the level of the normal person, have created a more frequent and prolonged asymptomatic as well as symptomatic complication — hypoglycemia, which has multiple adverse effects.

9. Although the true relationship of hyperglycemia to vascular degeneration is unknown, physicians should try to avoid induced insulin hypoglycemia.

10. Hypoglycemia as produced by the slow acting insulin, if of sufficient frequency, can be suspected of aggravating existing arteriosclerotic complications.

11. Of the two insulins — protamine zinc or globin insulin — globin insulin is preferred by the present investigators for control of the diabetic carbohydrate metabolism.

REFERENCES

1. Sindoni A., Jr.: Vitamin Deficiency in prescription Diets of Diabetics. *Amer. Jour. Dig. Dis. & Nutr.*, 3:759-765, (Dec.) 1936.
2. Friedman, G.: Cardio-vascular status of Diabetic Patient after the Fourth Decade of Life. *Arch. Int. Med.*, 55:371-397, (Mar.) 1935.
3. Root, H. F., Bland, E. F. and Gordon, W. H.: Coronary Atherosclerosis in Diabetes Mellitus. *J. A. M. A.*, 113:17-30, July 1, 1939.
4. Nathanson, M. H.: Coronary Disease in 100 Autopsied Diabetics. *Am. Jour. Med. So.*, 183:495-502, (April) 1932.
5. Proceedings of the New York Diabetes Association, Feb. 1944. *Amer. Jour. Dig. Dis. & Nutr.*, 11:345, (Nov.) 1944.
6. O'Brien, C. S. and Allen, J. H.: Ocular Changes in Young Diabetic Patients. *J. A. M. A.*, 120:190-192, Sept. 19, 1942.
7. Lisa, J. R., Magiday, M., Galloway, I. and Hart, J. F.: Arteriosclerosis with Diabetes Mellitus. A Study of the Pathologic Findings in 193 Diabetic and 2,250 non-diabetic Patients. *J. A. M. A.*, 120:192-195, Sept. 19, 1942.
8. Eisele, H. E.: The Juvenile Diabetic Patient Surviving Twenty Years. *J. A. M. A.*, 120:188-190, Sept. 19, 1942.
9. Laipply, T. C., Eitzen, O. and Dutra, F. R.: Intercapillary Glomerulosclerosis. *Arch. Int. Med.*, 74:354-364, Nov. 1944.
10. Zisserman, L.: Diabetes Mellitus. A Survey of 155 Deaths in Diabetic Patients. *Jour. Clin. Endoc.*, 1:314-315, April, 1941.
11. Trends in Mortality from Diabetes by State Death Rates per 100,000 and Percentage Change in 1940-1942 as compared with 1930-1932. American Diabetes Association — Diabetes Abstracts, 4:4, First Quarter, Jan. 1945.
12. Sindoni, A., Jr.: Blood Sugar Versus Urine Sugar. *J. A. M. A.*, 112:2503-2508, June 17, 1939 112:2595-2600, June 24, 1939.
13. Soskin, S.: Role of the Endocrine in the Regulation of Blood Sugar. *Jour. Clin. Endoc.*, 4:75-88, Feb. 1944.
14. Bernard, Claude: *Nouvelle Fonction du Foie*, Chez J. B. Bailliere, Paris, 1853.
15. Mann, F. C. and Magath, T. B.: Studies on the Physiology of the Liver. II. Effect of Removal of the Liver on the Blood Sugar Level. *Arch. Int. Med.*, 30:73, 1922.
16. Holmes, E.: *The Metabolism of Living Tissues*. University Press, Cambridge, 1937.
17. Osborne, T. B. and Mendel, L. B.: Nutrition and Growth on Diets Highly Deficient or Entirely Lacking in Preformed Carbohydrates. *Jour. Biol. Chem.*, 11:13, 1924.
18. Tsai, Chiao and Yi Chien Lung: Carbohydrate Metabolism of the Liver. III. The Sugar Intake During Glucose Absorption. *Chinese Jour. Phys.*, 8:273, (Aug.) 1934. II. The Sugar Output. *Chinese Jour. Phys.*, 3:245-272, (Aug.) 1934.
19. Goldblatt, M. W.: The Action of Insulin on the Glycogen Distribution in Normal Animals. *Biochem. Jour.*, 24:1199, 1930.
20. Hynd, A. and Rotter, D. L.: Studies in the Metabolism of Ani-

Sudden and Drastic Changes of the Carbohydrate Tolerance in Severe Insulin-Treated Diabetes

By

ARNOLD GALAMBOS, M.D.

and

WILHELMINA MITTEL MANN-GALAMBOS, M.D.

NEW YORK CITY

WHILE THE SIGNIFICANCE of the adjustment and the subsequent readjustments between the insulin and carbohydrate intake in diabetes mellitus is generally recognized, its high importance in cases with sudden and drastic changes in the carbohydrate tolerance in which a simultaneous sudden and drastic insulin readjustment is imperative, has not sufficiently been emphasized.

Mosenthal and Ashe (1) state: "It is obvious that from time to time nearly all diabetics require an adjustment of diet or insulin administration to the ever-changing carbohydrate tolerance. This may grow worse or improve, it may change remarkably for short periods with nervous upsets or minor infections such as coryza or digestive disturbances." One instance quoted by these authors as "very interesting" referred to a case in which at an unchanged diet 45 units of insulin were successfully reduced to 10, in the course of six weeks, without affecting the aglycosuric state. Joslin (2) described one of his cases of diabetes with acute onset as "remarkable" in regard to its carbohydrate tolerance improvement, when at an unchanged diet the discontinuance of the daily dose of eight units of insulin after six weeks failed to produce glycosuria.

Two cases presented here may cast light on the tremendous importance of the sudden and drastic carbohydrate tolerance changes — in both directions — within days or even hours. Failure of recognition, or correct interpretation of the new situation, and failure of an immediate and appropriate readjustment would have entailed not only danger to the patients, but might possibly have caused a fatal outcome.

CASE REPORTS

1) First case; J. S., 32 years, male, white; first seen on the 23rd of November, 1935.

Extremely stout man of 5 feet 11½ inches height, weighed 290 pounds. His diabetes had been detected six years ago, when acute balanitis with phimosis necessitated his seeking medical aid. Severe glycosuria had been found with an alleged blood sugar concentration of 0.20%. He reacted favorably to strict dietary regulation. Later he went off the diet.

Present complaints comprised: dry mouth, fetor ex ore, polydipsia, polyuria, nocturia. Patient estimated the daily amount of the urine at 3 or 4 gallons. All that was of no great significance to him, but since a week or so he had been troubled by the recurrence of the

balanitis with its accompanying phimosis, which caused him great distress. The dysuria and the acute suffering impelled him to seek medical aid.

In his past history gonorrhea with complicating epididymitis, suffered 8 years ago, was mentioned. The other side showed cryptorchidism.

The patient's parents and only sister are very stout. His mother is suffering from diabetes mellitus.

His physical examination was negative, except for obesity, which developed 9 years ago. Blood pressure was 150 systolic and 100 diastolic. The first sample of urine contained 14% of dextrose and a large amount of pus, which, however, originated solely from the preputial sack, which was greatly inflamed and full of bleeding rhagades. This caused swelling with consecutive phimosis, which permitted urination only in a thin stream, followed by agonizing pain. His blood sugar was 0.236%.

On account of a positive acetone reaction in his urine, 50 grams of carbohydrates daily were first allowed, with a simultaneously increasing scale of insulin administration. After three days, when daily 70 units of insulin were given, the urinary sugar was still 6%. By that time the general condition had improved considerably. Thereafter the patient was placed for three days on a near starvation diet, when, at a simultaneous increase in the insulin dose to 120 units daily (60 units twice) the urine became sugar free. After this had been achieved, carbohydrates were allowed to gradually increase to a daily amount of 90 grams, necessitating the simultaneous increase of the daily amount of insulin from 120 to 160 units. The total caloric intake remained considerably under the basal caloric requirement, totaling around 2200 Calories per day.

On this maintenance diet, with 90 grams of carbohydrates and 160 units of insulin, the patient did very well. The urine remained free of sugar, even the post-prandial samples. The blood sugar fell to 0.15%. Not the slightest reaction of a hypoglycemic nature was noted. By that time the local preputial condition had cleared up almost completely, the micturition became free, and the pain subsided. Only some slight degree of the phimosis was still present.

Six days after this equilibrium had been achieved (at 90 grams of carbohydrates and 160 units of insulin daily), the first complaints of a slight hypoglycemic reaction necessitated a moderate reduction of the daily insulin dose — at an unchanged diet. From this time on the changes developed rapidly. Readjustments became necessary, twice a day. During the following three days the amount of the insulin was halved, and after another three days insulin was completely discontinued — at an unchanged diet. The carbohydrate tolerance improved rapidly. The increase in the carbohydrate tolerance and the decrease of the insulin amount happened to be well balanced, their adjustment being and remaining correct throughout, which is conclusively proven by the

complete and permanent aglycosuria on the one hand, and the missed hypoglycemic reaction on the other. Thereafter the urine remained sugar free even after the increase of the daily amount of carbohydrates to 150 grams.

At this stage patient had to leave for Europe, on an important business trip, which was long overdue. Only my firm objection caused him to postpone this trip, from day to day, from the time of the highest insulin still when his trip was due. The danger of the continuation of the large amount of insulin at a time of diminishing demand, coincident with the rapid improvement in the carbohydrate tolerance, was only too obvious — it could have easily proved fatal.

COMMENT

There existed an unusual vicious circle between the diabetes mellitus and one of its complications, balanitis with its accompanying phimosis. As soon as the untreated diabetes deteriorated, itching and polyuria contributed to the recurrence of the balanitis, the patient being predisposed to it by a moderate phimosis, which latter condition as a result of the balanitis, became complete. The purulent, ulcerative balanitis deteriorated the carbohydrate tolerance of the diabetes to a great extent. This, in turn, increased the itching, the polyuria and the balanitis and phimosis. The proper treatment of the diabetes again improved the carbohydrate tolerance and this in turn, acting in the opposite direction, improved the entire chain of subsequent symptoms.

During the acute balanitis 100 units of insulin were needed to attain aglycosuria at a 90 grams daily K.H. intake, while during the dramatic improvement, coincident with the clearing up of the balanitis, in less than a week all the insulin became superfluous and daily 150 gms. of carbohydrates could be given, without glycosuria.

In this case a relatively minor local inflammatory process caused a tremendous deterioration of the carbohydrate tolerance — and the rapid healing of the local inflammation, again, created a dramatic improvement in the carbohydrate tolerance.

The amount of insulin, which together with a certain given diet, was necessary and essential to bring about an aglycosuric state, and was at the same time contributory to the clearance of the preputial inflammatory process, proved to be unnecessary, in fact, dangerous, at a moment of rapid change of events. The turning point in this case was arrived at at a time when the insulin has proved its efficacy. This might have easily changed a previously existing hyperglycemic condition into a dangerous hypoglycemic state. Close watch and immediate proper readjustment were necessary for a correct management of the case in a critical time, in view of the rapid change in the carbohydrate tolerance.

* * * *

2) Second case: J. G., 77 years, female, white; first seen and examined on the first of September, 1937.

Her diabetes had been incidentally discovered two years previously, during a routine urine examination. The symptoms were: polyuria, polydipsia, nocturia, itching skin mostly around the genitals, loss of weight of about 50 pounds, at a present weight of 98 pounds. Her gait became sluggish, uncertain, stiff, reminiscent of that of the paralysis agitans. Slight disorientation and occas-

ional mental confusion were noted. The amount of dextrose was stated to be around 5% in the urine. No blood sugar determinations were made. The patient received no treatment or dietary regulation.

Past history as well as family history revealed nothing of significance.

Physical examination revealed a high degree of arteriosclerosis. The peripheral arteries were found to be tortuous and rigid. Blood pressure was slightly elevated, averaging 165 systolic and 100 diastolic reading. Great emaciation and moderate dehydration were noted. The liver was smooth, sharp edged, ptotic, somewhat enlarged. Fluoroscopy revealed an elongated and tortuous ascending aorta and a moderate degree of emphysema of the lungs. The first sample of urine passed showed dextrose in 5% concentration. The blood sugar concentration was 0.38%.

Following a restricted diet for a few days, a more liberal diet was instituted. The diet consisted of 85 grams of carbohydrates and a liberal allowance of proteins and fats, totaling about 1600 Calories and representing an amount of 30% above her basal caloric requirement. Simultaneously, both insulin and protamine-zinc-insulin were administered on a slowly increasing scale. During five days on a regime with above diet and 60 units of insulin (20 units of insulin and 40 of protamine-zinc-insulin) the glycosuria decreased considerably and patient gained six pounds in weight.

In the course of the following few days a maintenance diet had been instituted. The carbohydrates were increased to 144 grams per day and the two types of insulin were substituted by the protamine-zinc-insulin alone in an amount of 70 units daily. Following this adjustment patient did very well; gained 14 pounds altogether. The urine, even in the post-prandial samples, became and remained free of sugar. There never was the slightest hypoglycemic reaction. The blood sugar read 0.15%.

This state was attained in 19 days, whereafter the patient received the protamine-zinc-insulin from a registered nurse in her home. She had been instructed to report any possible reaction or unusual observation.

The patient reported for a check-up and for a possible readjustment in two weeks and again in another five weeks. On each of these occasions several samples of urine were examined and found sugar free. The daily administration of 70 units of protamine-zinc-insulin was found to be perfectly well tolerated without causing the slightest hypoglycemic reaction. The carbohydrate tolerance seemed to be unchanged and no new adjustments were necessary.

On the 29th of November, 24 days after the last examination, the nurse wished to have some telephone advice, because "the patient did not want to get up, felt rather drowsy and could not move her right leg properly." These ominous symptoms prompted me at once to visit her. Upon my arrival, in less than one hour, I found the patient in coma. Lack of corneal reflex, stertorous breathing, deep cyanosis, involuntary micturition, etc., were present. Complete paralysis of the right lower and upper extremities was found, while the left side retained some slight muscular tone, in a mild catatonic state. The cardiac action was good, the pulse strong and rhythmic, the blood pressure read 150/100. Opisthotonus and Kernig signs were negative, Babinsky was over the right side slightly positive. The observations of the family and that of the nurse reaffirmed the fact that the first symptom noted was the paralysis of the right side.

On repeated questioning it was ascertained that the patient every day promptly received the dose of 70 units of protamine-zinc-insulin, the last administration being shortly before the onset of the coma. It was also established that she consumed her full diet every day, including 144 grams of carbohydrates. The patient had felt

very well, except during the last week when she had felt some slight dizziness, occurring mostly in the mornings. This dizziness was first mentioned now, it not having been considered of sufficient importance earlier for reporting.

Diagnostically first apoplectic stroke and diabetic coma had to be ruled out. The possibility of a hypoglycemic state must have occurred in one's mind, in spite of the fact that against such assumption militated the circumstance that the full, prescribed amount of the carbohydrates had been consumed and no premonitory or gradually increasing hypoglycemic reactions had been observed prior to the coma. On the other hand, again, some cumulative or late effect of the protamine-zinc-insulin, as well as a dietary error, though not admitted, might likewise have had precipitated symptoms, especially at a simultaneous, sudden and unexpected carbohydrate tolerance improvement. (Ashe, Mosenthal and Ginsberg (3) observed coma with hemiplegia in a case where only 5 units of insulin were given, 3 times daily. J. M. Ravid (4) observed a recurrent hemiplegia without coma, with recovery, in a hypoglycemic state after the administration of 62 units of insulin per day.)

There was not much time to be lost. I resorted to the intravenous administration of a hypertonic dextrose solution which, while not contraindicated in the first two conditions, is to be considered lifesaving in coma of hypoglycemic origin.

Blood taken for dextrose determination showed a concentration of 0.045%. This laboratory report affirmed the tentative diagnosis of a hypoglycemic coma, but being received "post festas," could not have been a factor in the diagnosis or in the therapeutic decision.

A 10% solution, on hand, was used for the intravenous injection. Hardly was the first 80 cc. injected when a sudden change occurred. The patient suddenly stirred. She opened her eyes and regained her consciousness. Her mind cleared up instantly and she gave intelligent answers to questions. The paralysis was gone. The total of 100 cc. was administered. Thereafter a forced carbohydrate feeding, through the oral and rectal route, was started. The patient received as much absorbable carbohydrates as she possibly could retain. She received about

150 grams of carbohydrates in food and in addition one quart of 5% dextrose was administered in Murphy's drip, between noon and evening.

Owing to the fact that instead of the regular insulin, protamine-zinc-insulin was administered, which may exert its maximal effect as late as 24 hours after its administration, a possible recurrence of the symptoms or a deterioration of the condition during the late evening hours was to be feared. And thus it happened. The patient again fell into a deep stuporous condition. A 10% glucose through the intravenous route, followed by the oral and rectal carbohydrate feeding acted similarly as once before. The following day the sensorium remained clear and the patient received carbohydrates by the mouth only. The first dextrose traces in the urine reappeared only two days later. The patient made an uneventful recovery; she was able to leave the house in a few days.

COMMENT

This case clearly demonstrates an unusual, sudden and drastic improvement of the carbohydrate tolerance. The unchanged, daily dose of protamine-zinc-insulin, which had been administered for about ten weeks, in an amount of 70 units per day, and which was properly adjusted to an unchanged diet for the same period of time, and which had not caused during this period even a mild hypoglycemic reaction, brought on, all at a sudden, without any premonition, a deep coma as the first manifestation of a hypoglycemic reaction. This tolerance improvement occurred rather dramatically, inasmuch as the patient about 12 hours prior to the onset of the coma felt so well that she went out on a social call. Only prompt evaluation of the situation with a subsequently prompt readjustment — in this case in the form of an intravenous dextrose injection — could have saved the patient from fatal consequences.

REFERENCES

1. Mosenthal & Ashe: Diabetes Mellitus: Tice's Practice of Medicine, Vol. IX, Chapter IV.
2. Joslin, Elliot P.: Treatment of Diabetes Mellitus. Lea & Febiger,

- Philadelphia and New York, 1923, 3rd Edition.
3. Ashe, Mosenthal and Ginsberg: J. Lab. Clin. Med., 1927-28.
4. Ravid, J. M.: Am. J. Med. Sc., 1928, Vol. CLXXV.

The Control of Diarrhea by Tomato Pomace

By

LESTER M. MORRISON, M.D.
LOS ANGELES, CALIFORNIA

DIARRHEA is one of the most frequent and distressing symptoms the physician is called on to treat (1). Any new agent successful in the therapy of diarrhea should be a valuable addition to the therapeutic armamentarium. It is the purpose of this paper to report the successful use of tomato pomace in the treatment of human diarrhea due to various causes.

At the present time, the most widely used inorganic preparations for diarrhea are represented by derivatives of opium, bismuth and kaolin. Pectin, particularly as scraped apple powder, has been used frequently in the diarrhea of children. The author has employed tomato pomace with excellent results in the treatment of diarrhea in both adults and children for a five year period.

In 1940, McCay and Smith (2) of the Animal Nutrition Laboratory, Cornell University, reported the anti-diarrheal effect of tomato pomace in a series of dogs, minks and foxes. They were so impressed by the striking anti-diarrheal action of tomato pomace, that they suggested its trial in human subjects suffering from diarrhea. McCay and Smith were able to control diarrhea within 24 hours by feeding 5% of the animal ration as tomato pomace and observed normal stools in the animals. An immediate recurrence of diarrhea in these animals could be produced at will by withdrawal of the tomato pomace; the stools could be made to return again to normal within 24 hours by the feeding of the tomato pomace. Analysis of the tomato pomace revealed a pectin content of only 3.8%, making it unlikely that the anti-diarrheal action is due solely to pectin. Since the report by McCay and Smith, the author has been unable to find any further report on this subject.

An editorial in 1943 appeared in the *American Journal of Digestive Diseases* which reviewed the work of McCay and Smith in animals and which expressed great interest in the possibility of using tomato pomace to stop diarrhea in the human patient. The editorial also suggested its trial in humans.

The tomato pomace used in this study was prepared by a process of tomato pulp dehydration. The pulverized product was ingested by a series of more than 100 patients at some time during a five year period. The tomato pomace was very pleasant to the taste and taken without difficulty. In the average case of diarrhea, the dose was one tablespoonful of the pomace in water on an average of every three hours; in severe cases of diarrhea a tablespoonful after each bowel movement was taken until the stools returned to normal.

The tomato pomace was used in the treatment of diarrhea from the following causes:

1. Idiopathic ulcerative colitis.
2. Food poisoning.
3. Infectious diarrhea such as so-called "intestinal flu," particularly as occurs in epidemic forms.
4. Food allergy (other than that to tomatoes).
5. Small intestinal hypermotility of idiopathic origin.
6. As an adjunct to antiamebicides and sulfonamides in amebic and bacillary dysentery.
7. As an adjunct to anti-parasitic treatment of intestinal worm infections.
8. Various diarrheas of reflex origin.
9. "Mucous" colitis.
10. "Spastic" colitis.
11. Diverticulitis of the colon.
12. Diarrhea from nutritional deficiencies.

In this series of patients with diarrhea, the average case had watery or mushy stools which ranged from three to ten daily. Occasionally, a patient had from ten to twenty diarrheal stools daily. Within 24 hours of the treatment with tomato pomace, many patients with diarrhea of simple or non-organic cause experienced a cessation of the diarrhea; after 24 hours the stools were noted to be of normal consistency, form, color and odor. Patients with diarrhea of great severity from non-organic causes would frequently require approximately 48 hours before the diarrhea was completely arrested and the stools returned to normal.

Microscopic examination of these stools after treatment with the pomace revealed the following: digestion appeared to be normal in respect to proteins, starches and fats. The routine fecal examination for these food-stuffs was made with acetic acid, lugol's stain and sudan III, respectively.

The specific pharmacologic action of the tomato pomace on the intestine does not appear to be clear at this time, but further studies on the question may clarify this point. Symptoms which frequently accompany diarrhea, such as abdominal bloating, cramp-like pains, distress, etc., when due to simple or non-organic causes, often disappear concomitantly with the diarrhea within 24 hours after treatment with tomato pomace. However, in cases with organic involvement of the intestinal tract such as ulcerative colitis, the tomato pomace does not exhibit rapid control of such symptoms as pain or distress, nor of the diarrhea, although the severity of symptoms in many cases is definitely ameliorated. This is also true of other anti-diarrheal medicinals.

It was frequently observed that diarrheal patients who received no relief from other currently used anti-diarrheal medication responded promptly to the tomato pomace, with a return to normal stools and disappearance of symptoms associated with the diarrhea. In

From the Gastro-Intestinal Clinic, Temple University Medical School and Hospital and the Division of Medicine, Philadelphia General Hospital.

Submitted October 11, 1945.

many patients without organic intestinal disease (such as ulcerative colitis) the diarrhea was frequently controlled within 24 hours (as was reported in animals by McCay and Smith).

Patients who are allergic to tomatoes obviously should not use the pomace. No toxic symptoms were observed; none being expected from fresh, unspoiled tomatoes.

As a side observation, it was noted that such gastric disturbances as pyrosis, epigastric distress, nausea and vomiting, belching, etc., were also frequently and promptly alleviated in many of the patients upon ingestion of the tomato pomace. This has been an old empiric observation of the laity, since tomato juice has been a traditional tonic "measure" on the morning after alcoholic excesses. The universal use of the tomato juice "cocktail" as an appetizer before meals is also an indication of the pleasantly stimulating or re-

freshing effect on the digestive tract of the tomato. A natural vegetable substance therefore such as herein reported is tolerated by the sick adult or child with intestinal hyperperistalsis and associated with digestive upset, at a time when the usual food or medication is repugnant to taste or sight.

SUMMARY AND CONCLUSIONS

1. Tomato pomace was employed in the treatment of various types of diarrheas described in a series of over 100 patients during a five year period of time.
2. Tomato pomace is an effective remedy in the treatment of many types of diarrhea in human subjects.
3. Diarrhea from simple or non-organic cause is usually arrested within 24 hours following treatment with tomato pomace.
4. In diarrheas not responding to anti-diarrheal medication, tomato pomace will often restore bowel movements to normalcy.

REFERENCES

1. Swalm, William A. and Morrison, Lester M.: "Diarrhea," *Cyclopedia of Medicine, Surgery and the Specialties*, F. A. Davis Co., Vol. 8, Part 1, pp. 1-20, 1940.

2. McCay, O. M. and Smith, S. E.: "Tomato Pomace in the Diet." *Science*, 91:388, April 19, 1940.
3. Editorial, *American Journal of Digestive Diseases*, 10:117 (March) 1943.

Case I, B. V., 43, male, 5-21-42. History: severe watery diarrhea (10 to 15 stools daily) of three days duration following ingestion of sea food (clams) which made two other family members similarly ill. First day of illness was accompanied by frequent nausea and vomiting. (Patient was previously treated by author for cholecystitis and diabetes mellitus.) **Physical examination:** Temperature 100.4 degrees; pulse rate 108; entire abdomen sensitive to palpation. Proctosigmoidoscopy essentially negative. **Routine Laboratory Tests:** 1. Complete blood count — negative. 2. Urinalysis — negative. 3. Blood Wasserman — negative. **Treatment:** One and one half ounces of castor oil on an empty stomach followed in two hours by one tablespoonful of tomato pomace with moderate quantities of fluids — every two hours; no solid food. **Progress:** Cessation of diarrhea within 24 hours of institution of tomato pomace treatment. Pomace continued for three days and then stopped; no recurrence of symptoms.

Case II, J. B., 44, male, 11-15-42. History: Passage of six to seven watery to mushy stools daily, with frequent abdominal distress; one week duration; emotional domestic problems; highly nervous. Past medical history essentially negative. **Physical examination:** Loss of five pounds in one week, marked weakness and lassitude; nervous tic of eyes. Temperature 98.4 degrees. Abdominal examination revealed essentially considerable tenderness to palpation along the entire palpable colon. **Routine Laboratory Tests:** 1. Complete Blood count — negative. 2. Urinalysis — negative. 3. Blood Wasserman — negative. 4. Stools — negative for ova and parasites. 5. Stools were negative for cultures re dysentery organisms. 6. Stools were negative for Bagen's diplostreptococcus. 7. BARIUM ENEMA: considerable spasticity and irritability of the large gut; no organic lesion. 8. Cholecystography — negative. 9. Gastro-intestinal X-ray series, upper — negative. **Diagnosis:** "Spastic (Psychogenic) colitis or (Spastic Colon Syndrome). **Treatment:** Tomato pomace, one tablespoonful every two

hours for one week. Phenobarbital gr. ½ four times daily; bland diet. ambulatory. **Progress:** After one day of above therapy, all symptoms disappeared, but medication continued for one week, then stopped. No recurrence of symptoms.

Case III, S. B., 63, female, 2-20-42. History: Diarrhea of ten days duration, consisting of six to eight stools daily; stools contain heavy amounts of mucus; vague constant abdominal distress throughout. Previous treatment for hypertensive cardiovascular disease. **Physical examination:** Blood pressure 185/110; temperature 98.4 degrees. Pulse rate 80; heart, accentuated A2 sound, enlargement of left ventricular border to mid-axillary line. Abdomen negative. Proctosigmoidoscopy: showed essentially congestion of mucous membrane of rectum and lower sigmoid colon with adherent mucus clinging in strands to the walls of the visible gut. **Laboratory findings:** 1. Complete blood count — negative. 2. Urinalysis — negative. 3. Blood Wasserman — negative. 4. Stools negative for ova and parasites. 5. Stools were negative for cultures re dysentery organisms. 6. Stools were negative for Bagen's diplostreptococcus. 7. Barium meal: organically negative. 8. Cholecystography: negative. 9. Upper gastro-intestinal x-ray series: negative. **Diagnosis:** Mucous colitis. **Treatment:** Tomato pomace one tablespoonful after every bowel movement; phenobarbital one half grain four times daily. Bland diet. **Progress:** Diarrhea stopped after fourth dose of pomace. One tablespoonful of pomace given three times daily for one week, then stopped. No recurrence of symptoms.

Case IV, H. B., 26, male, 3-29-44. History: Diarrhea of ten to twelve stools daily following milk diet for duodenal ulcer. If milk withdrawn diarrhea stops, but peptic ulcer pains become acute. Sleeplessness due to pain. (Soybean milk substitutes found very unpleasant to taste.) **Physical examination:** Markedly underweight (38 pounds). Great weakness and irritability. Marked pain to palpation in mid-epigastric area coinciding with ulcer zones. Proctosigmoidoscopy — negative. **Routine Labor-**

atory Tests: 1. Complete blood count — negative. 2. Urinalysis: negative. 3. Blood Wasserman — negative. 4. Stool studies — negative. 5. Gastro-intestinal x-ray series: Duodenal ulcer crater. 6. Gastric analysis — Grade 1 Hyperchlorhydria. **Diagnosis:** Diarrhea due to milk allergy during necessary peptic ulcer therapy. **Treatment:** Addition of Tomato Pomace one tablespoonful to each glass of milk given at the two hour intervals with patient in bed for three weeks. Phenobarbital grains one half four times daily. Tincture belladonna eight minims four times daily. Glass of milk and cream drunk at hourly intervals with Sippy diet. **Progress:** Within 12 hours of ingestion of tomato pomace, prompt cessation of diarrhea. This enabled the patient to undergo Sippy milk diet for healing of ulcer. Pomace continued in one tablespoonful, four times daily, doses for two months after the one week of pomace q. 2 hours. Normal bowel movements by patient throughout treatment. Ulcer symptoms disappeared in one week; healing shown by x-ray in three months; gain in weight of 35 pounds in three months.

Case V, C. B., 48, female, 1-13-43. History: Diarrhea of three days duration (7 to 10 stools daily) with so-called "intestinal flu" (during mild epidemic). Fever; aching pains in many joints of the body ("grippy sensation"). Confined to bed. Previously treated for chronic cholecystitis by author for four years. **Physical examination:** Temperature 101.5 degrees; pulse rate 126. Chest clear. Abdomen negative. **Routine Laboratory Tests:** Not done at home. **Diagnosis:** Intestinal virus infection (so-called "intestinal flu"). **Treatment:** Tomato pomace one tablespoonful every two to three hours. Empirin compound tablets No. 2 (B. W. Co.) one every three hours. Bland diet. Forced fluids. Bed rest. **Progress:** Diarrhea cessation within 24 hours. Fever and tachycardia continued for an additional five days, at which time pomace was withdrawn along with other medication since the infection had run its course. No recurrence of diarrhea.

Case VI, W. C., 48, male, 4-11-43. History: Six weeks duration of diarrhea, with passage of four to six stools daily, watery to mushy, slightly mucoid, with constant abdominal distress of indefinable character. Frequent "spells" of similar nature for previous five years, coming on every few months and related to nervous strain and emotional stress. Past medical history negative. **Physical examination:** Blood pressure 150/88; pulse rate 86; temperature 98 degrees; chest negative; abdomen very sensitive to palpation over entire length of colon. **Proctosigmoidoscopy:** Hypertonic anus; rectal spasm; mucoid mucosa of the rectum and lower sigmoid. **Laboratory findings:** 1. Complete blood count: Mild secondary hypochromic, normocytic anemia. 2. Urinalysis: slight traces of albumin. 3. Stools: negative for ova and parasites. 4. Stools — negative for dysentery organisms. 5. Barium enema: organically negative; marked spasticity throughout. 6. Gastro-intestinal x-ray series: essentially negative. 7. Gastric analysis: euclorhydria. 8. Cholecystography: negative. **Diagnosis:** Neurogenic colitis. **Treatment:** Tomato pomace one tablespoonful every three hours. Phenobarbital one-half grain four times daily. Bland diet. Ambulatory. **Progress:** Relief of diarrhea and abdominal distress in 24 hours. Treatment maintained for two weeks and then stopped. No recurrence of symptoms after six months.

Case VIII, M. G., 61, male, 7-24-43. History: Diarrhea of three days' duration, five days following anterior coronary occlusion with characteristic cardiac syndrome. Patient confined to bed and very ill. Five to six stools (watery) daily, extremely exhausting. Old gallbladder disease history. **Physical examination:** Temperature 99.6. Pulse rate 96. Cardiac status; sinus arrhythmia, presystolic apical murmur, and moderate enlargement of left ventricular border. Occasional fine crepitant rales at

both pulmonary bases. Rectal examination was negative. **Laboratory findings:** 1. Electrocardiographic changes characteristic of anterior artery occlusion. 2. Rapid blood sedimentation rate. 3. Moderate leucocytosis of blood count, 14,800. 4. Urinalysis — negative. 5. Stools negative for ova and parasites. 6. Stools negative to routine culture. **Diagnosis:** Coronary artery occlusion (anterior); old gallbladder disease (chronic calculous cholecystitis); reflex diarrhea. **Treatment:** Tomato pomace. One tablespoonful after each bowel movement; bed rest; liquid diet; papaverine one grain three times daily orally. **Progress:** Diarrhea controlled on second day; when tomato pomace withdrawn on fourth day, diarrhea promptly recurred. Maintained on tomato pomace for three weeks and tomato pomace withdrawn. No diarrheal recurrence. (Patient expired eight months later of recurrent coronary occlusion.)

Case VIII, A. G., 39, female, 2-9-42. History: Diarrhea of intermittent nature, lasting several weeks at a time, two to three times yearly for several years, associated with lower abdominal pains. Stools average six to ten daily during attacks. **Physical examination:** Temperature 97.4 degrees; pulse rate 68. Abdomen: very painful to palpation over the sigmoid colon area with local involuntary muscle guarding of the left lower abdominalis rectus muscle. **Proctosigmoidoscopy:** Excessive muscle spasm and congestion in the rectum not permitting examination of the sigmoid colon. **Laboratory findings:** Complete blood count — negative. 2. Urinalysis — negative. 3. Blood Wasserman — negative. 4. Stools were negative for ova and parasites. 5. Stools were negative for cultures re dysentery organisms. 6. Barium enema: Multiple diverticulae of the descending colon and sigmoid colon, with marked spasm and irritability of the sigmoid colon. 7. Cholecystography: negative. 8. Upper gastro-intestinal x-ray series: negative. **Diagnosis:** Diverticulitis coli. **Treatment:** Tomato pomace one tablespoonful every two hours for one day, and four times daily thereafter; discontinuation of previously used tincture of belladonna and pargoric (which had not been effective). **Progress:** Cessation of diarrhea within 24 hours with normal bowel movements thereafter. Discontinuation of tomato pomace in two weeks. No recurrence for three months.

Case IX, E. G., 33, female, 3-5-43. History: Diarrhea of one month's constant duration, with passage of blood and mucopus severe abdominal pains, loss in weight. Previously similar attacks occurred one to two times yearly, lasting from two to three months and diagnosed as "ulcerative colitis." **Physical examination:** Temperature 98.8 degrees. Pulse rate 92. Abdomen: marked tenderness throughout the entire abdomen. **Proctosigmoidoscopy:** Superficial mucosal erosions throughout rectal and lower sigmoid mucosa; scattered areas of gobs of mucus. **Laboratory findings:** 1. Complete blood count — negative. 2. Urinalysis — negative. 3. Blood Wasserman: negative. 4. Stools negative for ova and parasites. 5. Stools negative for cultures re dysentery organisms. 6. Stools negative for Bacteroides dysenteriae. 7. Barium enema: characteristic findings of non-specific ulcerative colitis. 8. Cholecystography: impairment of gallbladder function. 9. Upper gastro-intestinal x-ray series — negative. **Diagnosis:** Idiopathic ulcerative colitis. **Treatment:** Tomato pomace, one tablespoonful every two hours for one day, then four times daily thereafter. Supportive therapy of sulfasuxadine, vitamins orally and parenterally, phenobarbital and atropine sulfate, bland diet. **Progress:** Diarrhea controlled within 24 hours, with formation of soft stools daily, persisting in blood and mucopus content for one month. Pain moderately controlled. Tomato pomace continued for one month before discontinuation of all therapy concomitant with disappearance of symptoms.

Experiences in Non-Specific Diarrheal Conditions in the European Theater of Operations *

By

MAJOR WILLIAM J. HANES, M. C.

DEVON, PA.

ALTHOUGH the number of admissions to Army hospitals due to diarrhea is not so high, it has been a great source of morbidity among the fighting and service troops in the European Theater of Operations, thus impairing their efficiency. The "GI's," as the enlisted men have named this condition, is a symptom-complex for which most patients are treated in the unit dispensary. It is only the persistent and recurring cases or those associated with a violent onset or with some other condition that ever reach a general hospital, where this investigation was conducted. Although the cause of some cases of diarrhea is eventually traceable to a bacterial or parasitic infection, the cause for the majority of cases is never discovered.

This non-specific diarrhea, often accompanied by nausea and vomiting, is a condition seen not only in the Army, but, as Reimann and his associates (1) point out, is widespread and often epidemic in proportion occurring in schools, barracks, hospitals and hotels. It is often spoken of loosely as "intestinal flu" or "intestinal grippie," "acute infectious gastroenteritis," "seasonal gastroenteritis," etc. In his article Reimann does not make reference to the more persistent cases of diarrhea also encountered in this survey, but his description of the acute cases closely resembles that of the acute cases seen here.

In the paper the subject of diarrhea will be discussed under the following headings: 1) Unit Diarrheal Survey, 2) Clinical Investigation of Diarrhea, 3) Gastric Analysis Findings in Normal and Diarrheal States, and 4) Therapy in Non-Specific Diarrhea.

UNIT DIARRHEAL SURVEY

A questionnaire survey was conducted among personnel of a U. S. General Hospital (573 officers, nurses and enlisted men) with reference to the incidence of diarrhea and associated indigestion, the geographical incidence, the frequency of attacks, the duration of the episodes, and the possible relationship of diet to its etiology. It is realized that all types of diarrhea are of necessity included here and that, like all such surveys, the variable factors of individuals' reports — veracity, suggestability and mentality — must be taken into consideration. However, as the individuals concerned were in a medical unit, the responses to the questionnaire would be as accurate as could possibly be obtained.

It is to be noted (TABLE I) that 54% of the entire unit had diarrhea and 19% had indigestion without

TABLE I

Incidence of Diarrhea and Indigestion in Unit Personnel Since Being in the Army

	Total	Diarrhea	Indigestion	No Diarrhea or Indigestion
Officers	49	20 (40%)	11 (22%)	18 (38%)
Nurses	88	57 (64%)	18 (26%)	13 (20%)
Enlisted Personnel	436	235 (54%)	81 (19%)	120 (27%)
Total	573	312 (54%)	110 (19%)	151 (27%)

diarrhea since joining the Army; thus only 27% had no gastro-intestinal symptoms during that period. This illustrates an extremely high morbidity rate in individuals supposedly in a healthy age group (20-40). In the group with no gastro-intestinal complaints were most of the individuals used as controls referred to later in the paper.

As to geographical incidence (TABLE II), it is to be

TABLE II

Geographical Incidence of Diarrhea

	Total	Enlisted Personnel	Officers & Nurses
Individuals Having Diarrheal Episodes in United States (Variable Time Period)	61 (19%)	53 (22%)	8 (10%)
Individuals Having Diarrheal Episodes in United Kingdom (24 Month Period)	169 (54%)	124 (52%)	45 (58%)
Individuals Having Diarrheal Episodes in France (6 Month Period)	277 (89%)	206 (87%)	71 (91%)

noted that of those having diarrhea, whereas only 19% had diarrheal episodes in the United States, in comparison 54% had diarrhea in the United Kingdom and 89% in France. This illustrates statistically that the majority of individuals had their diarrheal episodes overseas. It is likewise of interest that in a comparison of the number of persons having diarrhea in the United Kingdom and in France, there was almost seven times as much diarrhea in the latter location compared to the former in a similar period of time. In accordance with this fact, there were approximately five times as many hospital admissions in France in this hospital due to unexplained gastro-intestinal upsets as compared to a like period of time in the United Kingdom. This is interesting in view of the fact that Army Field Ration "B," "C," "K," "K-10 in 1" and "D" were first used in the ETO on a large scale in France.

In investigating the frequency and duration of diar-

Submitted October 17, 1945.

*This clinical research was done under field conditions in 1944 and 1945 at the Second General Hospital in France.

rheal attacks in a 6 months' period in France (TABLE III), the following data were obtained: It was noted

TABLE III

Frequency of Diarrheal Episodes in France
(6 Month Period)

Diarrheal Episodes	Number of Patients	Total Diarrheal Episodes	Percentage
One Episode	135	135	49%
Two Episodes	25	50	27%
Three Episodes	34	102	12%
Four Episodes	10	40	4%
Five Episodes	6	30	2%
Six Episodes	7	42	2%
Over Six Episodes or Persistent	10	60	4%
Total	277	559	100%

that 49% had only one attack, whereas 51% had recurrences, 4% having it 6 times or more. Thus it may be assumed that over half of those who have a tendency to get this condition, get it often, whereas 27% of the unit never have been bothered, thus illustrating the factor of individual susceptibility. It is interesting to note that there were roughly 559 attacks in this one unit during a 6 months' period, once again demonstrating its prevalence. It was observed that the duration of the attacks was four days or less in 87% of the individuals studied, whereas in 13% the symptoms persisted from four days to over four weeks. As to treatment of these various attacks, 58% were self-treated, 32% were on sick-call or in quarters, and only 10% were hospitalized.

It was found that 63% of those with diarrhea had accompanying symptoms of indigestion (TABLE IV).

TABLE IV

Gastro-Intestinal Symptoms (Indigestion) in France

Indigestion with Diarrhea — 187 (61% of Diarrheal Patients)

Indigestion without Diarrhea — 110

Symptoms Complained of	277 Patients with Diarrhea	110 Patients without Diarrhea
1. Stomach Cramps	142 (51%)	57 (51%)
2. Excess Gas	164 (59%)	62 (56%)
3. Nausea	117 (42%)	47 (42%)
4. Anorexia	137 (49%)	52 (47%)
5. Fullness after Meals	106 (38%)	41 (37%)

As heretofore mentioned 19% of the entire unit had indigestion with no associated diarrhea. Their symptoms are listed along with the percentage of patients complaining of each symptom

CLINICAL INVESTIGATION OF DIARRHEA

1. *Method of Case Study.* In this study an attempt was made to correlate the symptomatology, physical findings and laboratory results with gastric dysfunction rather than explain the findings on the basis of an infection or inflammation. Thus 59 cases of acute and chronic gastrogenic diarrheas as well as 10 cases of chronic psychogenic diarrhea were thoroughly studied and followed, and an attempt was made to appraise the findings. The majority of the cases were hospitalized, although some of the acute cases were treated as out-patients. In each case analyzed a complete history was taken and a thorough physical examination was done. Laboratory work consisted of blood studies

(E.S.R., Hemoglobin percentage, W.B.C. and Differential), urinalysis and stool examination for ova, parasites and enteric pathogens. Gastric analysis was performed in each case, and in 20 cases this was repeated following therapy. It was impossible to do any virus studies in an attempt to rule out that possible etiologic agent. Whenever possible, and more especially in all chronic hospitalized cases, patients were instructed to keep a written diary with special reference to the number and character of their bowel movements, the presence or absence of abdominal cramps, mealtime anorexia and nausea and the effect of therapy instituted. These diaries were checked daily by the investigator.

2. Clinical Findings.

(a) Acute Gastrogenic Diarrhea (21 cases).

(1) *Typical Case Report* — A 34 year old soldier with 36 months in service, of which 32 months were spent overseas in England and France. Military occupation — hospital electrician. No previous history of gastro-intestinal complaints in U. S., although he had one previous similar attack in the U. K. and another two months ago in France. *Premonitory symptoms:* For week prior to acute onset patient had noted slight nausea and mealtime anorexia. *Onset:* Patient was awakened from sound sleep at 0200 hours with rather severe abdominal cramps, nausea, and watery diarrhea (4 brownish liquid stools). This was associated with loss of appetite. He experienced no chills or fever. He reported on sick call 7 hours after onset of diarrhea. *Dietary situation:* Patient has always had a fat intolerance but especially since being in the Army. At the time of this attack entire unit had been eating field ration "B" with all foods dehydrated or canned, and canned butter was being used on bread and in cooking. Patient noted an intolerance, especially for pork and fatty beef, which were prominent in the diet. At this time it might be noted there was an increase in the diarrhea rate among detachment personnel. *Physical examination:* The only positive findings were 1) exaggerated peristalsis and 2) abdominal distention. TPR normal. *Laboratory studies:* 1) Blood-W.B.C. 7500, with 76% Segs, 23% Lymphocytes, and 1% Eosinophiles; Hemoglobin 105%; E.S.R. normal; 2) Urinalysis — negative and 3) Stool — negative for pathogens, ova and parasites. 4) Gastric analysis:

	Free	Total
Fasting	8"	32"
After alcohol	0"	12"
After histamine	0"	8"

Note: Test was done 7 hours after onset of diarrhea.

(2) *Discussion of Findings:* These 21 cases were mostly from hospital detachment personnel and service troops served by this hospital, there being no combat troops studied or treated for such a mild complaint. Age limit varied from 21-40. Average duration of symptoms prior to seeking medical advice was 1-2 days. Symptoms consisted of acute onset of diarrhea, abdominal cramps and anorexia; in the majority of cases there was nausea but only a few experienced vomiting.

Practically all the cases had premonitory symptoms consisting of excess gas, belching and fullness after meals. The only physical findings of significance were exaggerated peristalsis and abdominal tenderness localized to the colon. Fever was uniformly absent. Blood, urine and stool examinations were routinely negative. Gastric analysis findings will be discussed later.

(b) *Persistent and Recurring Gastric Diarrhea (38 cases).*

(1) *Typical Case Report:* Combat infantryman age 25 with 10 months service, of which 2½ months were spent overseas in France. No previous gastro-intestinal complaints in U. S. *Premonitory symptoms:* Prior to onset of illness soldier noted excess gas, belching and flatus as well as a fullness in the epigastrium after meals. *Onset:* Acute onset of symptoms began 3 weeks after arrival in France. He was awakened suddenly from sleep with severe abdominal cramps, nausea, and vomiting, and profuse diarrhea (8-10 watery-brown movements). There were no fever or chills with the acute onset of this condition. Although extremely hungry between meals he noted a marked mealtime anorexia when food appeared before him. Diarrhea settled down to 6-8 watery-soft movements daily which were somewhat characteristic in that patient had a markedly exaggerated gastro-colic reflex resulting in a bowel movement in a matter of minutes after eating. Likewise he had an associated urgency of urination and rectal tenesmus resulting in voiding and defecating simultaneously. He noticed undigested food particles in his stool. Diarrhea persisted this way for 7 weeks during which time he became easily exhausted, restless, nervous and lost all ambition. All treatment—diet, sulfaguanidine, paregoric and bismuth proved to no avail. He lost 40 pounds during this time. *Dietary situation:* Patient stated he always had a fat intolerance but more so since his illness. Since being overseas he was first on "10 in 1 K" rations and later on field ration "B." *Physical examination:* The only positive findings were 1) obvious weight loss, 2) exaggerated peristalsis, 3) abdominal distention, 4) marked tenderness along the entire colon, especially at the flexure points and 5) TPR normal during hospitalization. *Laboratory studies:* 1) Blood-W.B.C. 5400 with 47% Segs, 43% Lymphocytes, 2% Monos and 8% Stabs, Hemoglobin 106%, E.S.R. normal, 2) urinalysis — negative, 3) stool negative for pathogens, ova and parasites, 4) Sigmoidoscopic examination — negative, and 6) gastric analysis:

	Free	Total		Free	Total
Fasting	0°	8°	Fasting*	0°	27°
1 hour after					
Histamine	25°	50°	After alcohol	0°	8°
2 hours after			Histamine		
Histamine	0°	8°	unavailable	-	-

*Note: Repeat gastric analysis 10 days after treatment with Dilute HCl.

(2) *Discussion of Findings:* These 38 cases represented almost all the branches of service overseas

equally divided between combat and non-combat troops. Age limit varied from 18-45. Average duration of symptoms when seen by this investigator was 8-10 weeks. The clinical picture was rather typical consisting of acute onset of abdominal cramps, profuse diarrhea (8-10 liquid brown movements), nausea and vomiting usually preceded by a week of premonitory symptoms — excess gas, belching, and fullness after meals. The diarrhea then became persistent — 6-8 watery-soft foul smelling bowel movements daily characteristically occurring post-prandially. Attention is called to the associated urgency of urination and rectal tenesmus resulting in simultaneous voiding and defecation. The diarrhea seemed to be most common in the early morning when the patient first became active. Stools contained undigested food particles. These diarrheal symptoms are not characteristic of this type of diarrhea only, but when present are merely indicative of chronically disturbed and hyperactive gastro-intestinal physiology from whatever cause it may be — infestation, chronic infection, deficiency states, etc. Associated symptoms encountered were weight loss (average of 15 pounds in all cases studied), exhaustion, hunger between meals, mealtime anorexia, and fat intolerance. The only positive physical findings were 1) weight loss, 2) exaggerated peristalsis, 3) borborygmus, 4) abdominal distention and 5) localized abdominal tenderness along the entire colon. TPR was consistently normal. Stool and urine examinations were consistently negative. Blood studies likewise were negative except for a persistently seen eosinophile count averaging 2-3% which may or may not be of significance. In one case a sigmoidoscopic examination was performed during the acute phase of the diarrhea and the mucosa resembled that seen in acute ulcerative colitis. In those in which gastro-intestinal x-ray series, barium enema studies and proctoscopy were done, all were reported negative. Unfortunately, no gastroscopic studies were done in these cases because the equipment was not available. It is hoped that this can be done to ascertain if there is any acute or subacute gastritis present in these cases which might be related and responsible for the gastrogenic etiology of this condition.

(c) *Persistent and Recurring Psychogenic Diarrhea (10 cases).*

(1) *Typical Case Report:* Combat infantryman, age 22, with 2 years' service, 5 months of which have been overseas. Two previous prolonged hospitalization periods since arriving in France in October, 1944 for the same complaints. No previous history of gastro-intestinal complaints in U. S. *Premonitory symptoms:* None prior to original acute onset but between diarrheal episodes he experienced fullness in abdomen and excess gas. *Onset:* Patient was well until October 24, 10 days after arrival in France, when he suddenly developed severe abdominal cramps, nausea, vomiting and watery diarrhea (10-12 bowel movements). He was evacuated to the aid station and to an evacuation hospital where his symptoms subsided on light diet, paregoric and sulfaguanidine. However, immediately on

returning to the line he developed persistent diarrhea and recurring vomiting episodes, especially "when the going got tough." The diarrhea in the chronic phase was characteristic — 1) post-prandial due to the exaggerated gastro-colic reflex, 2) coincident urination and defecation due to urgency of urination and rectal tenesmus, 3) diarrhea occurred most frequently in the morning and 4) undigested food was seen in the stool. Although always hungry, patient complains of mealtime anorexia. He also noted weakness, exhaustion, and nervousness to be present along with slight weight loss, these associated symptoms being increasingly manifest as his diarrhea persisted. *Dietary relationship:* Acute onset developed after exposure to "C" and "10 in 1 K" ration for 10 days. He noted a mild fat intolerance and was unable to eat canned butter. *Physical examination:* The only positive findings were 1) exaggerated peristalsis, 2) tenderness along the entire colon but especially the ascending and descending portions and 3) the fact that he was a very nervous and apprehensive individual. *Neuropsychiatric appraisal by Psychiatrist:* Constitutional psychopathic state with emotional instability and inadequate personality. Recommend limited assignment. *Laboratory findings:* 1) Blood W.B.C. 13500, 75% Segs, 23% Lymphs, 2% Eosin, E.S.R. normal, 2) urinalysis — negative, 3) stool — negative for ova, parasites and pathogens, 4) gastric analysis:

	Free Before HCl	Total 35°	Free After HCl	Total 15°
Fasting	10°	35°	0°	15°
After alcohol	5°	25°	0°	20°
After Histamine	35°	75°	-	-

5) B.M.R. plus 9%.

(2) *Discussion of Findings:* It was felt to be significant that, with the exception of one individual, all the ten cases studied were combat infantrymen. This soldier gave a history of recurring attacks of "colitis" in civilian life. Age limit varied from 19-31. Average duration of symptoms when seen by this investigator was 5-6 weeks. The clinical picture in these cases closely resembled that seen in chronic gastrogenic diarrhea, once again indicating a disturbance of normal gastro-intestinal physiology. In these cases the etiology was on a psychogenic basis since all of these patients on consultation with a psychiatrist were proven to be cases of psychoneurosis with anxiety state (Combat Exhaustion) or constitutional psychopathic state, and their symptoms were felt to be merely manifestations of their psychiatric conditions. Urine and stool examinations were consistently negative. Except for an average eosinophile count of 4-5%, all blood studies were likewise within normal limits. In several of these cases, gastro-intestinal x-ray series, Barium enema studies and proctoscopy were performed and all reports were consistently negative.

GASTRIC ANALYSIS FINDINGS IN NORMAL AND DIARRHEAL STATES

1. *Method Employed:* Using a Levin tube intranasally, the fasting specimen was withdrawn, following which 50 cc. of 7% ethyl alcohol was instilled as a test

meal. At the end of one hour a second specimen was withdrawn. When available, 0.25 mg. of Histamine phosphate was injected hypodermically and one-half hour later a third specimen was removed.

2. *Interpretation of Results:* It is pointed out in most standard textbooks on the subject that whatever the regulatory mechanism of gastric secretion may be, the fact remains that the acidity of gastric contents varies widely in different individuals and in the same individual at different times, covering practically the entire range of concentration theoretically possible. They agree, however, that 3% of normal males (age 20-30) show an absolute anacidity, and that a deficiency of HCl occurs in approximately 10-15% of the general population. Although normal values vary in even the standard textbooks, the following were used as criteria in this study:

Normal — 20° - 70°)
Hypoacidity — less than 20°) 20-40 age limit
Hyperacidity — greater than 70°)

Anacidity

- Basal Anacidity — No free HCl in fasting specimen
- Relative Anacidity — No free HCl in fasting and test meal specimen
- Absolute Anacidity — No free HCl in fasting, test meal specimen, or after injection of Histamine

3. *Controls (TABLE V):* Gastric analyses without the use of Histamine (unavailable) were performed on 24 medical corpsmen and patients who on questioning stated they had never had any gastro-intestinal complaints at any time in the Army. It is to be noted that these soldiers have for the most part been on a similar diet to those having diarrhea since being in France. The average free HCl in the fasting specimen of these controls was 26° and in the specimen after alcohol test meal was 23°. Five cases of the 24 had a basic anacidity, although 3 of these had bile present in the first specimen which some authors claim contaminates the specimen, and were thus not included in the above average. In none of the 24 cases was there demonstrated a relative anacidity. Using the above standard it was felt that in the fasting specimen or with alcohol test meal, 8 of the cases (33%) revealed a hypoacidity whereas the remaining 16 cases (67%) were within normal limits. An interesting point which is felt to be significant is that in one control case, having never had gastro-intestinal complaints previously, 5 weeks later entered the hospital with a typical episode of acute gastrogenic diarrhea with nausea and vomiting. He had shown a hypoaacid response when tested as a control (10° in fasting specimen and 12° after alcohol) and with his illness his gastric analysis revealed a relative anacidity with only a 12° response following Histamine injection.

4. Diarrheal States:

(a) *Acute Gastrogenic Diarrhea (21 cases):* Gastric analyses were performed on 21 cases of acute diarrhea (TABLE V). It was noted the average free HCl in the fasting specimens was 10° and in the specimen after alcohol test meal was 14°; however, there

was a normal response in 16 cases studied after the use of Histamine, averaging 33°. Analyzing these cases from another point of view, 10 of the 21 cases (50%) showed a basic anacidity, 7 of the 21 cases (33%) showed a relative anacidity, and 3 of the 16 cases (18%) in which Histamine was used showed an absolute anacidity. In the fasting specimen, or upon response to test meal, 13 of the 21 cases (62%) showed hypoacidity or anacidity, whereas, 8 of the 21 cases (38%) showed normal gastric analysis findings. 12 of the 16 cases (75%), when Histamine was used, demonstrated a latent normal acidity, showing that acid is present although probably temporarily depressed for some reason. It is interesting to note, in relation to the length of time gastric analysis was done after onset of diarrhea, that in 6 cases examined less than 24 hours after onset of symptoms the average free HCl in fasting specimen was 5°, after alcohol test meal 4°, and after Histamine 8°; whereas in 15 cases examined from 24 hours up to 7-10 days after onset of diarrhea

(27%) an absolute anacidity. In the fasting specimen or upon response to alcohol test meal, 29 of the 34 cases (86%) showed an anacidity or hypoacidity, and in 5 of the 34 cases (14%) there were normal gastric analysis findings. With Histamine 8 of the 18 cases (44%) illustrated a normal HCl response, again indicating the acid is present but depressed temporarily.

(c) *Persistent and Recurring Psychogenic Diarrhea (10 cases)*: Gastric analyses were performed on 10 cases of persistent and recurring cases of diarrhea and the findings tabulated in TABLE V. It will be noted that the average free HCl in the fasting specimen was 13°, in the specimen after alcohol test meal 15° and after Histamine 36° (6 cases). Analyzing these findings from another point of view it will be seen that in only 2 of the 10 cases (20%) was there a basic anacidity, in only 1 of the 10 cases (10%) was there a relative anacidity, and in only 1 of the 10 cases (10%) was there an absolute anacidity. In the fasting specimen or upon response to alcohol test meal 7 of the 10

TABLE V
Comparative Gastric Analysis Findings in Controls and Diarrheal States

Gastric Analysis Findings	Controls (24 Cases)	Acute Gastro- genic Diarrhea (21 Cases)	Chronic Gastro- genic Diarrhea (38 Cases)	Chronic Psycho- genic Diarrhea (10 Cases)	Chronic Specific Diarrhea (6 Cases)
Normal*	67%	38%	14%	30%	100%
Hypoacidity or Anacidity*	33%	62%	86%	70%	0%
Hyperacidity*	0%	0%	0%	0%	0%
Total	100%	100%	100%	100%	100%
<i>Histamine Response</i>					
Normal	-	75%	44%	66%	100%
Hypoacidity or Anacidity	-	25%	56%	17%	0%
Hyperacidity	-	0%	0%	17%	0%
Total	-	100%	100%	100%	100%
<i>Anacidity</i>					
1. Basic**	8%	50%	71%	20%	66%
2. Relative**	0%	33%	53%	10%	0%
3. Absolute**	-	18%	27%	10%	0%
Average Fasting Specimen (HCl in degrees)	26	10	3	13	9
Average Specimen after Alcohol (HCl in degrees)	23	14	7 (34 cases)	15	22
Average Specimen after Histamine (HCl in degrees)	-	33 (16 cases)	20 (18 cases)	36 (6 cases)	38 (4 cases)

* Findings in fasting or test-meal specimens only.

** An individual could have a basic, relative and an absolute anacidity, thus explaining apparent percentage discrepancies.

the average free HCl in fasting specimen was 12°, after alcohol test meal 18°, and after Histamine 38°. This might be interpreted as an attempt on the part of gastric physiology to return to normal spontaneously, as manifested by a more normal production of HCl.

(b) *Persistent and Recurring Gastrogenic Diarrhea (38 cases)*: Gastric analyses were performed on 38 cases of persistent and recurring cases of diarrhea, and the findings are tabulated in TABLE V. It will be noted that the average free HCl in fasting specimen was 3°, after alcohol test meal 7°, and after Histamine 20° (18 cases). Analysis of these findings from another point of view discloses that 27 of the 38 cases (71%) revealed a basic anacidity, 18 of the 38 cases (53%) a relative anacidity, and 5 of the 18 cases

cases (70%) showed an anacidity or hypoacidity and 3 of the 10 cases (30%) revealed a normal response; however, 5 of the 6 cases (83%) with Histamine gave a normal or hyperacid response, once more showing the acid is present in these cases, although latent.

(d) *Chronic Specific Diarrhea (6 cases)*: Although no attempt was made to study specific diarrheas in relation to gastric analysis findings, there is presented for comparison the gastric findings in six cases of chronic afebrile diarrhea which, because of the disturbance of gastro-intestinal physiology, closely resembled the clinical picture of the chronic gastrogenic diarrheal cases in this series. There were 2 cases of hookworm infestation, one with roundworm infestation, 2 cases of chronic bacillary dysentery (Flexner type) and 1 case

of idiopathic sprue studied. It will be noted (TABLE V) that the average free HCl in the fasting specimen was 9°, in the specimen after alcohol test meal 22°, and after Histamine 38° (4 cases). Regarding anacidity in 4 of the 6 cases (66%) there was a basic anacidity; however, none showed a relative or absolute anacidity. In the fasting specimen or upon response to alcohol test meal, all cases showed a normal HCl response as did the 4 cases in which Histamine was used. These figures are presented merely for information and present insufficient data on which to base any deduction or conclusion relative to differential diagnosis in chronic diarrhea.

(e) *Comparison of Gastric Analysis Findings Prior to and After Therapy with Dilute HCl (TABLE VI):*

TABLE VI

Comparison of Free HCl Findings (in Degrees) in Gastric Analysis Before and After Treatment

Gastrogenic Cases

Before Treatment After Treatment

Patient	Dose of HCl	Days on Treatment	Fasting	After Alcohol	After Histamine	Fasting	After Alcohol	After Histamine
Case 2	1 cc	14 Days	0	18	None	0	0	5
Case 4	1-4 cc	9 Days	0	0	None	0	0	0
Case 5	1 cc	7 Days	0	0	None	0	0	10
Case 9	1 cc	9 Days	12	0	27	0	10	30
Case 10	1 cc	7 Days	9	0	None	37	14	None
Case 12	1 cc	7 Days	22	23	None	0	0	None
Case 14	1 cc	7 Days	0	13	None	18	0	None
Case 15	1 cc	9 Days	0	0	None	4	36	None
Case 16	1 cc	14 Days	0	0	None	0	0	None
Case 17	1 cc	6 Days	0	19	None	0	13	None
Case 18	1 cc	7 Days	8	11	None	0	15	None
Case 19	1 cc	9 Days	0	5	None	0	22	None
Case 3	1-4 cc	7 Days	0	0	None	31	0	47
Case 28	1-2 cc	14 Days	0	0	5	0	0	None
Case 25	2 cc	7 Days	0	-	25	0	0	None
Case 24	1 cc	10 Days	0	0	None	8	16	None
Average in 16 Cases			3	6	19	6	8	18
			(3 cases)		(5 cases)			

Psychogenic Cases

Before Treatment After Treatment

Patient	Dose of HCl	Days on Treatment	Fasting	After Alcohol	After Histamine	Fasting	After Alcohol	After Histamine
Case 5	1-2 cc	12 Days	10	6	35	0	0	None
Case 1	1 cc	7 Days	12	22	None	22	6	None
Case 2	1 cc	7 Days	10	16	None	20	5	None
Case 3	1 cc	7 Days	17	20	None	12	37	None
Average in 4 Cases			12	16	35	13	12	None

Gastric analysis was performed on 16 cases of chronic gastrogenic diarrhea and 4 cases of chronic psychogenic diarrhea prior to and after 7-10 days therapy to determine the effect, if any, on the amount of HCl present in the gastric juice. As shown by Rose (2) in patients with achlorhydria, the customary doses of 1-2 cc. of dilute HCl produced no demonstrable change in pH or peptic activity and was not followed by any recoverable free acid production. It required 4-8 cc. to

produce recoverable free acid to change the pH significantly and to affect peptic activity. As can be seen from consulting TABLE VI, there was no appreciable change in the free HCl findings following therapy, which would in itself account for the action of HCl when good therapeutic results were obtained.

THERAPY IN NON-SPECIFIC DIARRHEA

1. *Plan of Therapy:* In each case in which Dilute HCl (U.S.P.) was used it was employed in dosages of 1-2 cc. in 30 cc. water with each meal for a period varying from 7-10 days. In some cases a placebo of lemon juice powder (2 gms. to 30 cc. water) was used prior to the addition of the acid so that these patients did not know when or if the acid was present, this being done to rule out any possible psychic effect of the remedy. In several resistant cases a dosage of 4 cc. in 60 cc. water was used but it was felt no added benefit was obtained by the increased dosage. In several cases medication was given prior to meals with the same effect as that derived with meals. It is suggested that the dosage be gradually reduced (0.5 cc. each day) rather than suddenly stopped, since diarrhea recurred in several cases when the latter was done. To keep other factors in therapy to a minimum, all cases were treated on a regular diet and on an ambulatory status. In a few cases fat-free diets were tried, but no added benefit seemed to be derived from this so that plan was discarded.

2. *Results of Therapy:*

(a) *Acute Gastrogenic Diarrhea:* Obviously, if nothing were done in the majority of these cases, diarrhea would subside, and it was accordingly felt that no improvement in diarrhea in these cases could be attributed to HCl. However, 17 of the 21 cases studied had premonitory symptoms of mild indigestion—fullness in abdomen after meals, excess belching and flatus and abdominal cramps. These symptoms were uniformly relieved in all these acute cases, which outcome fits in with the known fact that this form of therapy often relieves the vague gastro-intestinal complaints associated with hypacidity.

(b) *Persistent and Recurring Gastrogenic Diarrhea:* It is in these cases that the best results of therapy were noted as TABLE VII discloses.

(1) *Diet, Hospital Rest and Placebo (Therapy Controls):* In these cases the improvement was attributed to the general rest obtained, which in itself stopped the vicious circle present in these cases. This illustrates the fact that HCl is not required in all such cases; however, in the more resistant cases, it became evident that rest alone would not suffice; in these cases, therefore, HCl was given to advantage (DIAGRAM 1).

(2) *Diet, Hospital Rest and Placebo to which HCl was added after 2-4 days:* In these cases, as TABLE VII reveals, there was no response to the placebo alone, but when dilute HCl was added, 11 cases showed a dramatic response; in one case the response was fair, and in 3 cases there was either no response or the results obtained were felt to not be due to the medication. In the failures on treatment, it was felt all

psychogenic factors were ruled out. The reason for the persistence of symptoms could not be ascertained.

(3) *Diet, Hospital Rest and HCl (No Placebo)*: In this group of cases HCl dilute was used in 1-2 cc. dosages in 30-60 cc. water. There was dramatic im-

(c) *Persistent and Recurring Psychogenic Diarrhea*: Although the results in these cases have not been tabulated, it can be said that in every case there was no response to HCl therapy. In 9 of the 10 cases, after psychiatric consultation, it was felt that these

TABLE VII
Therapy Employed and Results in Chronic Gastrogenic Diarrhea

Patient	Response to Previous Therapy	Treatment Employed in this Study	Effect on Diarrhea	Effect on Associated Indigestion	Time of Response
Case 11	None	Regular Diet — Hospital Rest — Placebo (7 Days)	Improvement	Improvement	2 Days
Case 22	None	Regular Diet — Hospital Rest — Placebo (7 Days)	Improvement	Improvement	1 Week
Case 13	None	Regular Diet — Hospital Rest — Placebo (3 Days)	Improvement	Improvement	2 Days
Case 27	None	Liquid Soft Diet — Hospital Bed Rest	Improvement	Improvement	1 Week
Case 23	None	Soft Diet, Fat-Free Diet—Placebo (7 Days)	Improvement	Improvement	2 Days
Case 12	None	Placebo for 2 Days — Regular Diet	Improvement	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 19	None	Placebo for 2 Days — Regular Diet	None	None	2 Days
		Dilute HCl (9 Days) — Regular Diet	Improvement	Improvement	
Case 14	None	Placebo for 2 Days — Regular Diet	None	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 10	None	Placebo for 2 Days — Regular Diet	None	None	1-2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 33	None	Placebo for 4 Days — Regular Diet	None	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 2	None	Placebo for 2 Days — Regular Diet	None	None	5-7 Days
		Dilute H Cl(14 Days) — Regular Diet	Improvement	Improvement	
Case 5	None	Placebo for 2 Days — Regular Diet	None	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 3	None	Placebo for 2 Days — Regular Diet	None	None	
		Dilute HCl (10 Days) — Regular Diet	None	None	
Case 4	None	Placebo for 2 Days — Regular Diet	None	None	
		Dilute HCl (10 Days) — Fat-Free Diet	None	None	
Case 28	None	Placebo for 2 Days — Regular Diet	None	None	
		Dilute HCl (14 Days) — Fat-Free Diet	None	None	
Case 34	None	Placebo for 2 Days — Regular Diet	None	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 35	None	Placebo for 3 Days — Regular Diet	None	None	2 Days
		Dilute HCl (9 Days) — Regular Diet	Improvement	Improvement	
Case 36	None	Placebo for 3 Days — Regular Diet	None	None	2 Days
		Dilute HCl (9 Days) — Regular Diet	Improvement	Improvement	
Case 37	None	Placebo for 3 Days — Regular Diet	None	None	2 Days
		Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	
Case 38	None	Placebo for 2 Days — Regular Diet	None	None	2 Days
		Dilute HCl (10 Days) — Regular Diet	Improvement	Improvement	
Case 8	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 9	None	Dilute HCl (14 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 15	Temporary	Dilute HCl (9 Days) — Regular Diet	Improvement	Improvement	1 Day
Case 16	Temporary	Dilute HCl (10 Days) — Regular Diet	Improvement	Improvement	Delayed
Case 17	None	Dilute HCl (6 Days) — Regular Diet	Improvement	Improvement	1 Day
Case 18	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 20	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	1 Day
Case 21	None	Dilute HCl (14 Days) — Regular Diet	Improvement	Improvement	1 Day
Case 24	None	Dilute HCl (6 Days) — Regular Diet	Improvement	Improvement	5 Days
Case 25	None	Dilute HCl (10 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 26	Temporary	Dilute HCl (14 Days) — Regular Diet	Improvement	Improvement	3 Days
Case 29	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 31	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	2 Days
Case 32	None	Dilute HCl (7 Days) — Regular Diet	Improvement	Improvement	2 Days

provement in 13 cases and a fair response in one case (Case 8); in the latter the response was delayed as the patient was edentulous in addition to having a relative anacidity, thus further interfering with normal digestion.

patients should be reassigned to non-combat duty. Within a week after this decision was definitely established, improvement was noted. Thus one may say that gastro-intestinal balance was once again established after the conflict had been removed. It might be added

that in these cases diarrheal stools were examined by either the investigator or his ward sergeant to rule out the possibility of malingering.

(d) *General Discussion on Results of Therapy:* One factor not to be minimized in importance in the treatment of these cases is the use of the regular well-balanced hospital diet. No attempt has been made to prove HCl is indicated in every case of diarrhea, even

be given 1-2 weeks in order not to miss a response in a resistant case and also to be sure that the normal gastric balance is firmly established.

One can easily see why the medication itself fails to get at the real trouble in psychogenic diarrhea, since the essential difficulty resulting in the gastro-intestinal imbalance is neurogenic or psychogenic, in other words extra-gastric, whereas in the other cases the essential

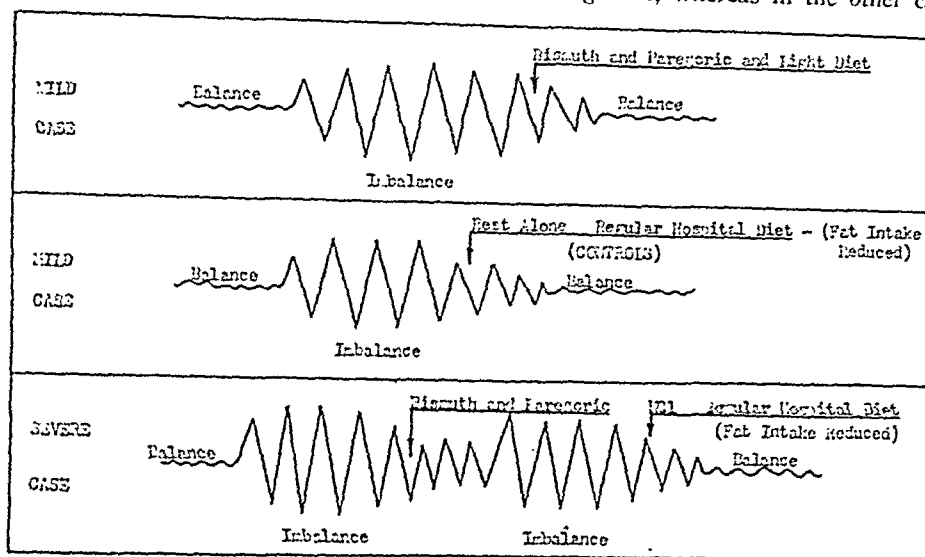


DIAGRAM I

Schematic Presentation of Therapeutic Effect on Diarrhea

in the persistent cases, as can be seen by the above therapeutic results and the accompanying diagram (DIAGRAM 1). The use of this remedy in the treatment of persistent diarrhea is not new; merely its application in these cases of persistent and recurring diarrhea occurring in France is presented. As this study illustrates, since this common disorder might well be on the basis of gastric dysfunction, rather than on an infectious or virus basis, then it is felt the use of this purely physiologic remedy is warranted. It is felt that it is indicated in those persistent afebrile cases not helped by diet and hospital rest alone and in whom there is not an obvious psychogenic component. It was felt that the response can be attributed to the HCl, since there was no effect on the placebo medication, and a response occurred within 24-48 hours after HCl was added.

Improvement in these cases was manifested by cessation of diarrhea, abdominal cramps, borborygmus and nausea, as well as a return of mealtime appetite. There was an associated gain in weight and disappearance of exhaustion and easy fatigability. Physically there was noted, parallel with symptomatic improvement, a subsidence of localized and generalized abdominal tenderness as well as abdominal distention. In 3 cases the response was delayed for 3-5 days but this was unusual. In this series of chronic cases whose average duration of symptoms had been 8-10 weeks and, who had failed to respond to any previous medication, it was observed that if any improvement was to occur from this form of therapy it would be manifested rather dramatically within 48 hours; however, it should

trouble is gastrogenic or intra-gastric. In the latter case there result disturbances of gastric secretion and motility due to some unknown cause which will be discussed later in the paper. Since these cases of gastrogenic and psychogenic diarrhea present an almost identical end-result of aberration of normal gastro-intestinal physiology, often time alone will tell into which classification a given case belongs. However, it was felt that in this clinical study, although there was no yardstick by which one could measure the psychiatric component, the complete lack of response to any therapy including HCl was strongly in favor of its psychogenic etiology.

Unfortunately, due to the exigencies of war, adequate follow-up of the cases treated was impossible; however, it is known that in six of the chronic gastrogenic diarrheal cases, there was mild recurrences of symptoms, each time promptly relieved by HCl medication.

COMMENT

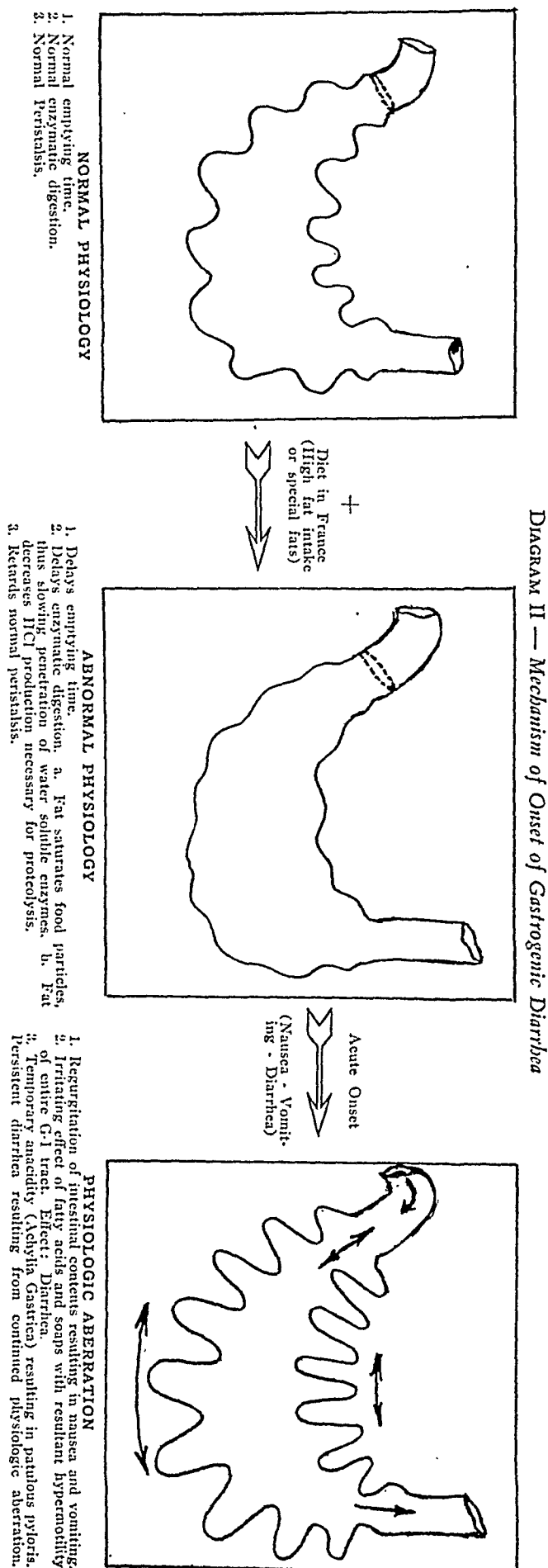
1. *Etiologic Factors:* The etiology of these acute and chronic non-specific cases is still undetermined. Reimann and his associates (1) in a recent article describing the acute form of what might be the same condition, suggest the possibility of it being a filterable virus which is airborne and gains entry through the gastro-intestinal tract; however, he admits he is unable to isolate this virus or transmit the disease. Those that feel this condition is due to a virus will with some reason argue that perhaps the hypoacidity, proven to be present in these cases, is the result of the infection rather

er than possibly related to diet. With 51% of the individuals in the diarrhea survey having recurrences, this would be some evidence against it being a virus disease, since in most virus disease immunity is conferred by one attack. In Reimann's study (1) as in this investigation all the usual laboratory procedures failed to reveal any bacterial etiologic agent.

In this study it was felt that this entire group of symptoms and physical findings might be explained on the basis of disturbed gastric physiology. Consequently, certain known facts in relation to anacidity and a high fatty diet or possibly a concentrated diet containing long-chain, high melting-point fats were investigated. The effect upon one another and upon gastric digestion was studied with the idea that perhaps therein lay the answer to these acute and chronic gastro-intestinal up-sets.

(a) *Effect of Increased Fat Intake or Concentrated Diet (containing high melting-point fats):* Wolf and Wolff (3) refer to Beaumont's observation that oily substances remained in the stomach for a relatively long period of time. Recently they confirmed this fact that fat with meals not only prolongs emptying time but actually inhibits acid secretion and gastric motility. The standard physiology textbooks agree with these observations. Bloor (4) in a recent article states that fats are, with few exceptions, well digested, well absorbed and well utilized if taken in moderate amounts with other foods. When taken in larger proportions in the food, fats cause disturbances which are the result of several factors. They coat or saturate other food materials and in that way slow penetration of water-soluble digestive enzymes. They slow the enzymatic and muscular activity of the stomach, retard its emptying and may produce discomfort and finally regurgitation of intestinal contents into the stomach. Fats may cause diarrhea due probably to the volume of liquid produced when melted or to the fact that the fatty acids or soaps produced by digestion are irritating to the intestine. In regard to specialized long-chain, high melting-point fats, McLester (5) refers to Langworthy's work who noted that in general when the melting point of fats is high (this depending upon the length of the chain and the number of double bonds in the molecule) digestion is slower and there is a tendency for unabsorbed fats to appear in the feces. Fats with a melting point above 37.8° Centigrade were more slowly absorbed and a laxative effect was noticed with such things as cocoa butter and beef fat when used in excess.

In this regard the following related facts are presented for consideration. Troops in this theater for the most part had never been exposed to concentrated army field rations on a large scale until D day. Diarrhea did not present itself as a problem among the fighting and service troops until the arrival of the troops in France where it was necessary in the conduct of offensive warfare to employ such rations. Reference is made especially to the relatively high fat content of "10 in 1 K" ration (170 gms. fat) and the "B" ration (149 gms. fat). Although the individual total fat content of "C" (77 gms. fat), "D" (95 gms. fat) and



"K" (115 gms. fat) is not high, in its usage it was recommended that the "C" and "K" ration be supplemented with the use of "D" bar, thus raising the relative fat content of the diet. Of course it may not be the amount of the fat but rather the type of fat used in the concentrated diets for there is present long-chain high melting-point fats in special items common to most of the concentrated and canned diets — canned butter served and used in cooking (containing hydrogenated vegetable fat), "D" bar (containing cocoa fat) and "K" and "C" ration biscuits (containing hydrogenated vegetable fat in the shortening used in their preparation). As stated above these synthesized fats with a high melting-point could act as a source of irritation to the gastro-intestinal tract.

Pursuing the subject further in this respect in the questionnaire survey of the personnel of a general hospital, it was noted that 64% of the individuals who had diarrhea noted a relationship to the diet in France, the majority of these noting especially the "C" ration and the continued use of "B" ration. Likewise, 86% of the individuals who had indigestion noted a relationship to the diet in France; once again the majority noted it especially with "C" ration and the continued use of "B" ration. It was a fact that during two different periods in which nothing but canned and dehydrated "B" ration was served to the unit along with canned butter there was a marked increase in the amount of diarrhea.

(b) *Premise or Working Hypothesis* (DIAGRAM 2) — Keeping the above facts and observations regarding fats and anacidity in mind, the following theory is proposed for consideration to explain the causative factor in the development of acute and chronic gastrogenous diarrhea. With the excess fat intake or an intake of a foreign long-chain fat abnormal gastric physiology results in time that the emptying time, enzymatic digestion and gastric motility are delayed. This results eventually in a sudden onset of gastro-intestinal symptoms (nausea, vomiting and diarrhea) due to 1) regurgitation of intestinal contents; 2) hypermotility of the entire gastro-intestinal tract due to the irritating effect of fatty acids and soaps and 3) a patulous pylorus associated with the resulting temporary anacidity. There consequently results a vicious circle (temporary achylia gastrica) due to physiological aberration manifesting itself in the clinical picture of gastrogenous diarrhea — exaggerated gastro-colic reflex, exaggerated peristalsis, etc.

The exact role fats or special fats have in the causation of this type of non-specific gastrogenous diarrhea requires further investigation before any conclusions can be drawn. The question of the effect of diet is a complicated one since it is not what is issued to the soldier but what he actually eats that is the important factor. It is hoped that these clinical observations will act as a stimulus to experimental investigators having at their disposal facilities for more detailed study as well as access to the literature in order to more fully understand the etiology and treatment of this condition

of disturbed gastric physiology so prevalent in the armed forces overseas.

(c) *Individual Variable Factor in the Causation of Diarrhea* — Presumably those with a normal gastric acidity or even those with a low or absent acidity when on a normal well-balanced diet might develop no gastro-intestinal disturbances (situation in the United States or in United Kingdom). Whereas, given the same conditions and add the concentrated army field rations, relatively high in fats or containing special type fats acute gastro-intestinal conditions may develop in some individuals abruptly or in time due to cumulative action. Thus, when a certain threshold is reached, the balance of normal digestion in susceptible individuals may be upset as described in the manner above (DIAGRAM 2). This would be in accord with the fact that the control cases, in contrast to the diarrheal cases, illustrated an average normal acid secretion, perhaps indicative of the fact that their normal level had been higher than that previously and had not reached a low enough level in them to be productive of symptoms. In this regard it will be recalled that in one of the control series in which a later gastric analysis was performed when the patient had his first attack of diarrhea in the ETO, this patient showed a hypoacidity response when symptom-free and a relative anacidity when symptoms were present on admission. In this study only 3 of the 38 cases of chronic gastrogenic diarrhea had any symptoms prior to their leaving the United States for overseas. It was observed that some of these patients, after varying lengths of time (usually 2-3 weeks) following their arrival in France and resultant exposure to army field rations, developed acute gastro-intestinal symptoms preceded by premonitory symptoms of indigestion. Another frequent observation was that diarrhea was noted in units when there was a sudden change from "K" and "C" ration in the front line to all cooked "B" ration meals in rest camps; in these cases the sudden change in the type of diet plus overeating may be the factors responsible for embarrassing normal digestion.

In this connection, it was noted quite often whenever French soldiers or German prisoners were first exposed to U. S. Army field rations diarrheal outbreaks and indigestion were quite commonly encountered in individuals who had previously been asymptomatic. This was likewise seen in repatriated American, Russian and British prisoners of war, some of whom undoubtedly had a hypoacidity secondary to starvation and malnutrition during their long periods of confinement. The sudden change in diet again prompted embarrassment in gastric physiology with resultant gastro-intestinal complaints.

This hypothesis would explain the individual factor in this so-called "epidemic" of diarrhea in this theater, why one develops symptoms while another exposed to the same food and living conditions does not. Likewise, it would explain why, since the men of a unit, in a hospital or in a re-inforcement pool are on the same type of rations, that this would appear to occur in "epidemics," when actually it might be that their in-

tolerance for concentrated and fatty foods was becoming manifest at the same time with resultant disturbed gastric physiology.

(d) *Extraneous Factors further disturbing Gastric Physiology:* Best and Taylor (6) pointed out that physical fatigue and certain emotional states — apprehension, fear, mental strain, shock or depression — tend as a rule to inhibit peristalsis and reduce gastric tone. Wolf and Wolff (7) showed that fear and emotional conflict (represented by the anxiety state in the combat cases in this study) will delay gastric emptying time; likewise fear and withdrawal were found to be accompanied by mucosal pallor, hypoacidity and hypomotility in the stomach. Obviously these are factors that are present in a theater of war and must be taken into consideration. These few facts illustrate some of the many complex and interwoven mechanisms at work affecting gastric digestion and why, therefore, any study of this nature or any results of therapy are difficult of interpretation.

2. *Suggested Pharmacological Action of Dilute HCl in Chronic Gastrogenic Diarrhea:* The standard textbooks of physiology, pharmacology and medicine refer to the use of Dilute HCl in persistent diarrhea (gastrogenous) and in diarrhea associated with achlorhydria such as in pernicious anemia. However, the method of its action is not clear. All authors are in agreement that any action it might have is not due to the change in the gastric acidity, in which fact this investigator concurs (TABLE VI).

It is assumed for the moment that in these chronic cases of gastrogenic diarrhea there is a disturbance in gastric physiology resulting in hypermotility and hyperperistalsis. There is also presumably a patulous pylorus in association with a temporary or relative anacidity (DIAGRAM 2), this situation resulting in premature and rapid emptying of the stomach of only partially digested food, especially proteins. With this situation present when medication is used, it is suggested that perhaps it acts in the following way: Beckman (8) states that HCl acts by 1) improving tonus and peristalsis, especially that concerned in gastric evacuation, 2) by releasing pepsin from pepsinogen of the glands and 3) by promoting an acid medium for the action of pepsin on the protein molecule during proteolysis. Wolf and Wolff (9) have shown in a human subject who had a gastrostomy, that when Dilute HCl ranging from 0.02 Normal to 0.33 Normal HCl was introduced through a tube into the stomach, these acids were found to exert an inhibitory effect upon gastric contractions proportional to their strength. 0.33 Normal HCl for example inhibited gastric contractions for 30 minutes. It was noted in the experiment that the inhibition was effected most readily in the phase of hypermotility. The strength of the dosage used in this group of cases when properly diluted was as follows: 1) 1 cc. in 30 cc. (0.039 Normal) and 2) 2 cc. in 30 cc. (0.078 Normal). This is interesting in view of the opinion now widely held that the pylorus is patent for the greater part of the time and that evacuation of the stomach is definitely related to the peristaltic activities

of the antrum; thus the decrease in the peristaltic activity by the HCl may secondarily affect closure of the pylorus.

Consequently, the HCl may act locally by its mere presence in inhibiting hyperactive peristalsis. It might thus act as a governor in establishing normal gastric tone and peristalsis and break up the vicious circle of gastric imbalance which is present. There then would result a situation favorable to normal gastric digestion, especially proteolysis. Clinically this hypothesis was borne out by the dramatic response many of these patients had following use of this remedy.

SUMMARY

1. A questionnaire survey was conducted of the personnel of a United States General Hospital overseas and statistical data relative to diarrhea and indigestion is presented (TABLES I-IV inclusive).

2. A group of 21 cases of acute gastrogenic diarrhea as well as 38 cases of chronic gastrogenic diarrhea and 10 cases of chronic psychogenic diarrhea were investigated and the results of the clinical findings analyzed in reference to history, positive physical findings and laboratory results. With the exception of gastric analysis findings, all laboratory studies were consistently negative. A typical case report has been presented for each type of diarrhea and the findings in each group discussed.

3. Gastric analysis studies were done on all of these patients as well as on 24 normal controls who had never had gastro-intestinal complaints since being in the army (TABLE V). In sharp contrast to the controls, there was a noted hypoacidity, being most noticeable in the chronic gastrogenic cases, many of which showed a relative anacidity. There was no apparent relationship, however, between the degree of hypoacidity and anacidity and the duration or severity of symptoms. In most cases a normal response was brought forth with histamine so that the anacidity appeared to be temporary or relative rather than absolute. Gastric analysis findings in 6 cases of chronic specific afebrile diarrheas are presented for comparison.

4. Except for the 10 psychogenic cases, it was felt the diarrhea was primarily on a gastrogenic basis because of the clinical syndrome they presented and the altered findings on gastric analysis indicating disturbed gastric physiology. Consequently, therapy with Dilute HCl was instituted based on known pharmacological facts regarding its usage in gastrogenic diarrhea. A possible pharmacological action of Dilute HCl was proposed.

5. The results of treatment with Dilute HCl in 29 cases of persistent gastrogenic diarrhea resistant to all other forms of therapy were most encouraging. Dramatic clinical improvement, usually within 48 hours, was noted in 24 cases (83%), fair results in 2 cases (7%) and failure to respond to treatment was noted in only 3 cases (10%). None of the chronic psychogenic cases responded to this form of treatment and the possible explanation for this is presented. In the acute cases, although undoubtedly the diarrhea would

have subsided if nothing were done, all of the cases were relieved of their associated symptoms of indigestion in addition to the cessation of the diarrhea.

6. The etiology of these acute and chronic non-speci-

fic afebrile diarrheas is still undetermined. A theory as to its possible dietary etiology based on facts and observations presented in this clinical investigation is submitted.

REFERENCES

1. Reimann, H. A., Hodges, J. H. and Price, A. H.: Epidemic Diarrhea, Nausea and Vomiting of Unknown Cause. *J. A. M. A.*, 127:pp. 1-5, January 1945.
2. Rose, E.: Personal communication.
3. Wolf, S. and Wolff, H. G.: *Human Gastric Function*, pp. 133-139. Oxford University Press, New York City, 1943.
4. Bloor, W. R.: Fats in Metabolism, *Nutrition Reviews*, 2:289, October 1944.
5. McLester, J.: *Nutrition in Health and Disease*, p. 151, W. B. Saunders, Philadelphia, 1937.
6. Best, C. H. and Taylor, N. B.: *The Physiological Basis of Medical Practice*, p. 787, Williams and Wilkins Co., Baltimore, 1939.
7. Reference 3, pp. 66, 130 and 137.
8. Beckman, H.: *Treatment in General Practice*, p. 507, W. B. Saunders, Philadelphia, 1942.
9. Reference 3, pp. 37-39.

Editorial

HISTORY OF MEDICINE

GEORGE ROSEN believes that currently there is an increased interest in all history (and therefore in the history of medicine) because, having passed through a disastrously traumatic phase of world history, we are instinctively prompted to look back in the hope of picking up some of the provocative antecedents of our "brave new world." Undoubtedly this element of acute retrospection is now operative particularly with respect to social and political systems, but perhaps less so in medical science, because physicians usually feel that Medicine, throughout its course, has done rather well, and cannot often be accused of having made frankly disastrous decisions. Now, as always, the chief

utility of a medical historic document is the pleasure it affords the true medical scholar and the value it contributes to medical reference. As Rosen points out, medical progress is part of general culture, and there have been several striking advances in medicine during the past decade. We have all been busy keeping up with current technical developments and have neglected the history of medicine. But owing to man's habitual tendency to fluctuate rhythmically between work and meditation, we may expect soon a re-awakening of interest in the medical past. *The Journal of the History of Medicine and Allied Sciences** under Rosen's editorship has appeared, and Vol. I. No. 1 is notable not only for its interesting contributions but for its unusually attractive format. Unlike the *Bulletin of the History of Medicine*, it will not deal with bibliographies or papers of a philological nature, but rather with subjects of wide medical interest.

*Published quarterly by Henry Schuman, 20 E. 70th Street, New York 21, N. Y., \$7.50 per year.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
*J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

* With the Armed Forces.

CLINICAL MEDICINE

BOWEL

MOREHEAD, R. P. AND WOODRUFF, W. E.: *Solitary giant follicular lymphoma of the vermiform appendix.* (Arch. Path., v. 40, p. 51, 1945).

Symptoms simulating those which occur in acute appendicitis led to operative removal of the appendix in three patients. The appendix was found to have a restricted tumor involving the lymphoid tissue. Hyperplasia of the lymph nodules, and invasion of the different layers by large hypochromatic cells, smaller chromatic cells, and lymphocytes, characterized the tumors. The tumors were classified as giant follicular lymphoma with direct transformation into polymorphous cell sarcoma. Although only one tumor was found in each appendix it is uncertain whether others were not present in the viscera which were not explored. — H. Stilyung.

JAFFE, R.: *Explanation and classification of appendicular lesions.* (Rev. Sudamer. Morfol., v. 2, p. 28, 1944).

The author maintains that vascular alterations (anemia or hemorrhage) play a fundamental part in the origin of appendicular inflammations, because they in turn produce alterations of the glandular epithelium, making it vulnerable to germs or toxins. He reviews the acute, catarrhal, and the chronic forms of appendicitis and describes the genesis of the appendix-copathies. — Courtesy of Biological Abstracts.

CORBETT, E. U.: *The visceral lesions of measles. Koplik spots in the colon.* (Am. J. Path., v. 21, p. 905, May, 1945).

In measles there are more widespread lesions of the viscera than has been suspected. Although lymph tissue involvement, such as the changes in the appendix, has been reported, giant cell formations in the viscera have been seen rarely. Giant cells in lymph nodes and in the colon and ileum of a fatal case of measles are described. Small eosinophilic cytoplasmic inclusions in the giant cells, bronchial mucous glands, and oral sub-mucous glands in regions of the Koplik spots are described in several fatal cases of measles. The author believes that the inclusion bodies are not necessarily

specific of measles since these or similar bodies are also found in other virus diseases. — H. Stilyung.

PANCREAS

WAUGH, J. M., DIXON, C. F., CLAGETT, O. T., BOLLMAN, J. L., SPRAGUE, R. G. AND COMFORT, M. W.: *Total pancreatectomy. A symposium presenting four successful cases and a report on metabolic observations.* (Procced. Staff Meet. Mayo Clinic, v. 21, p. 25, Jan. 1946).

Two of the four cases discussed had total pancreatectomy performed because of hyperinsulinism due to islet cell adenoma, one, because of carcinoma of the head of the pancreas in a patient with diabetes mellitus and one because of chronic fibrous pancreatitis with calcification. Postoperative metabolic studies were performed on all cases. Comparisons were made with the depancreatectomized dog. In humans, diabetes mellitus was established within 18 to 24 hours postoperatively but was readily controlled by moderate doses of insulin. With insufficient insulin ketosis developed. There was a loss of approximately one-half of the ingested fat and one-third of the ingested nitrogen in the feces, the stools showing 2.5 to 7 times the normal nitrogen content and 5 to 7 times the normal fat content. There was a loss of 22% to 34% of the caloric intake in the feces and urine. There was normal digestion and absorption of carbohydrate. Although pancreatectomized dogs show approximately a 50% fall in plasma lipids, no significant fall was found in the human cases. The bromsulfalein hepatic function test was normal in three cases tested. The patients were kept in a relatively healthy state by the use of a high protein, high carbohydrate, moderate fat diet with the use of plain and protamine zinc insulin, and pancreatin 15 gms. per day. The case of carcinoma later developed metastases and one of the cases of adenoma died during an insulin reaction resulting from an excess of insulin, after returning home. The authors feel that total pancreatectomy should be performed in cases of islet cell tumor of the head of the pancreas, carcinoma of the pancreas, in chronic pancreatitis if more conservative measures fail and in diffuse cystadenoma because of the danger of malignant change in this latter condition. — E. J. Tallant.

LIVER AND GALLBLADDER

MONAGHAN, J. F.: *Evaluation of liver function tests.* (Penn. Med. J., v. 48, p. 1036, Oct. 1945).

Since the liver performs various functions, each of the various liver tests evaluates the efficiency of only a particular function. Valuable information may be obtained from six tests: galactose tolerance, hippuric acid excretion (sodium benzoate conjugation), retention of bromsulfalein, urinary urobilin, albumin-globulin ratios, and the effect of vitamin K on prothrombin formation. According to Monaghan, determinations of serum bilirubin and of icterus only suggest that there exists a liver dysfunction while the six tests are specifically designed to aid in the differential diagnosis of the liver disease. — D. A. Wocker.

THERAPEUTICS

ELSON, K. A., PEPPER, D. S. AND FORRESTER, J. S.: *The treatment of bacillary dysentery in Chinese soldiers with sulfaguanidine and sulfadiazene.* (Am. J. Med. Sc., v. 211, 1946).

This is a report on the treatment of 334 Chinese patients with a relatively benign form of bacillary dysentery. One-third received a placebo, one-third sulfaguanidine, and one-third sulfadiazine. The clinical course was not affected by the administration of either drug as compared to the placebo-treated controls. The duration of fever, the number of daily bowel movements and the duration of illness appeared essentially the same in all three groups.

The authors admit that their results are completely at variance with other reports and offer two possible explanations; one, that the treatment was begun on the average five days after the onset of symptoms and since the disease untreated usually lasts two weeks and the dysentery organism disappears quite rapidly from the stool, little if any, beneficial effect could be expected. However, there were considerable numbers where the treatment was begun on the first or second day and these also failed to show any clinical response.

The second possible explanation offered was that since the disease had a very mild course with no deaths, the beneficial effects of drug therapy were difficult to measure in objective terms. This explanation is also deemed probably inadequate because there were a sufficient number of cases with sufficiently severe symptoms in which the response to drug therapy also was nil.

The authors emphasize the fact that these observations in no way should preclude the treatment of dysentery with the sulfonamides, inasmuch as it has been definitely shown that the use of these drugs markedly reduces the incidence of the carrier state following the disease.

No toxic effects were noted with the use of sulfaguanidine, but in ten instances gross urinary complications resulted in cases receiving sulfaguanidine. Three of these became anuric and two required ureteral lavage. — C. De Berardinis.

SURGERY

LAM, C. R.: *Surgical treatment of congenital atresia*

of esophagus: report of four cases. (J. Pediat., v. 27, p. 456, Nov. 1945).

If congenital atresia of the esophagus is suspected the use of barium for diagnosis should not be attempted since the barium irritates the bronchial mucosa. Iodized oil, introduced by catheter and removed after roentgenograms have been taken, is advocated. There need be no haste to operate since correction is not necessarily an emergency operation. The operation should be performed only by a competent thoracic surgeon. Early diagnosis permits both sufficient time to obtain the services of a good surgeon and leads to measures preventing aspiration pneumonia. Lam reports on four infants operated for congenital atresia with survival and excellent results in three. Early diagnosis enabled operation to be carried out on the three surviving infants while they were still in excellent condition. — D. A. Wocker.

METABOLISM AND NUTRITION

MADDEN, S. C. AND WHIPPLE, O. H.: *Amino acids in the production of plasma protein and nitrogen balance.* (Am. J. Med. Sc., v. 211, p. 149, 1946).

In both dogs and human patients the 10 essential amino acids were found to be effective in plasma protein production when these were the sole source of protein intake. These can be given by mouth, by vein, subcutaneously or intraperitoneally. They are very efficacious in maintaining weight and nitrogen balance. The amino acids can be given rapidly in 10% solution parenterally with little or no clinical disturbance, but glutamic acid in digests or amino acid mixtures is not well tolerated by vein and may cause vomiting.

The experiments were conducted on standardized hypoproteinemic dogs depleted of circulating plasma protein and reserve protein by plasmapheresis. It was found that by limiting the dietary protein intake to 1 gram per kilo body weight, the daily removal of 20% of the circulating plasma reduces the plasma protein level from the normal to 4% in one to three weeks. Subsequent variations in the kind and quantity of protein intake are reflected in the amount of plasma protein that must be removed to maintain a steady hypoproteinemia.

The authors comment upon the fact that therapy with amino acids is much more flexible than with protein digests in that it is reasonable to suspect that injury of a specific tissue might be most rapidly repaired by a mixture of amino acids corresponding to that tissue. — C. De Berardinis.

SADOWSKY, A. AND DIAMONT, J.: *Contribution to the problem of vitamin B₁ deficiency during pregnancy.* (Acta. Med. Orientalia, v. 2, p. 203, 1943).

In 75 cases comprising normal patients, pregnant women, women during and after birth, pregnancies with vomiting, pre-eclamptic and other pathologic cases, no marked vitamin B₁ deficiency was found by the pyruvic acid method. — Courtesy of Biological Abstracts.

Present Trends in Mucous Colitis

By

HARRY GAUSS, M.D.
DENVER, COLORADO

MUCOUS COLITIS is considered to be a functional disorder of the colon neurogenic in origin characterized by the excessive secretion of mucus in the stools, by marked irritability and spasticity of the colon, by excessive flatulence, localized or diffuse abdominal pain and diverse constitutional symptoms.

The present trend is to consider it essentially a neurosis of the colon, a form of psychosomatic disease which expresses the individual's conflict with his environment wherein he has suffered some frustration or defeat, following which, the external conflict became manifest as some psychic phenomenon as fear, anxiety, worry, etc., which in turn was mediated through the sympathetic nervous system to the bowel to produce functional derangements and symptomatology in the colon.

Hurst (1) objects to the use of the term "mucous colitis" on the grounds that it is not a true inflammation, rather it is a dysfunction in which mucus appears in the stools. Be it as it may, the term "mucous colitis" enjoys common usage to designate the syndrome described in this paper. Further, the old ideas of sharply differentiating organic from functional disease are melting away in the light of the modern concepts of psychosomatic medicine which predicates that functional disturbance gives rise to cellular disease and this in turn to structural alterations. In short there is no longer a line of demarcation between functional and organic disease. One merges into the other. Some writers would even go further and declare that this is a reciprocal reaction that functional disease gives rise to organic changes but also that structural alterations give rise to functional changes, in this manner producing some of the vicious cycles of which mucous colitis is an example. Thus the presence of an anxiety state may result in mucus in the stools, while the presence of mucus in the stools may incite an anxiety state thus establishing a vicious cycle.

ETIOLOGY

Mucous colitis occurs in early adult life, commonly in the twenties and in the thirties. In White and Jones' (2) series, the average age of their patients was 35 years, while the average age at the time of onset was 23 years. This also indicates the chronic nature of the disease. Some people suffer from its annoyances all of their adult life. Women are affected more frequently than men in the ratio of about five to one.

It is definitely associated with psychoneurotic states especially high tension personalities, with anxiety

states, adjustment problems, submerged fear complexes, guilt feeling, inadequacy, etc.

It often merges with the syndrome of irritable or spastic colon. Indeed at times it is difficult to differentiate between the two except by the presence of mucus in the stools and the severity of the symptoms. Eggleston (3) states that "I sometimes find it difficult to differentiate between mucous colitis and spastic colon except by the amount of mucus." Further this relationship is suggested by the similarity of their etiologic factors, since in both there occurs a disturbance in the equilibrium of the sympathetic and parasympathetic control of the colon.

The anatomic basis of the neurosis is found in the elaborate nervous innervation of the colon which upon examination is seen to contain 1) a vegetative nervous system, the plexus of Auerbach which lies within the wall of the colon which is capable of causing contractions of the intestine even when all of the nerves of the intestine are completely separated from all outside connector fibers, 2) it receives connector fibers from the pelvic nerve, a parasympathetic nerve which arises from the first, second and third sacral roots, and 3) it receives connector fibers from the sympathetic plexes located in the superior mesenteric ganglion, inferior mesenteric ganglion and pelvic ganglion. Through these three nerve systems, the colon is in relayed contact with practically every part of the body including the psychic processes, and thus comes under the influence of all metabolic processes of the body as well as the psychic activities.

The present trend is to consider mucous colitis a neurosis of the body which has localized in and caused dysfunction of the secretory and motor mechanisms of the colon.

Elsewhere we (4) have pointed out that the causes of a neurosis are manifold, complicated and prolonged in their genesis. "It is seldom that a single incident produces a neurosis although it may appear to do so. Actually it was only the precipitating factor. Adequate inquiry into the behavior problems of the individual will usually show that there was present a sequence of events which prepared the individual for the precipitating factor."

The three principal predisposing etiologic factors which are usually present in the development of any neurosis are: heredity, environment, and training. These comprise the so-called neuropsychopathic triangle. This neuropsychopathic triangle helps to explain why all individuals do not react to a given situation in the same manner. There are multiple influences at work

in the individual, with no two persons reacting in exactly the same manner to a given situation.

Conflict with the environment or some life situation is the immediate precipitating factor in the pathogenesis of a neurosis.

When such conflict occurs, the biologic response within the individual is the primitive instinct of fear. Fear in itself is not a menace as it is a basic mechanism for self preservation in the life of the individual. It operates in the process of survival. Fear is a normal process, but it becomes abnormal when it occupies a place out of proportion to the actual threat of the safety to the individual. Then it becomes pathologic, and pathologic fear gives rise to worry, inadequacy and anxiety states, and so initiates the mechanism of a neurosis.

When fear is experienced, its impulse is mediated to the sympathetic nervous system, which transmits it in turn to the several viscera thereby causing functional changes in these organs which in turn are capable of causing cellular changes and finally gross alterations. Chronic fear or worry thus becomes a tyrannical master over the body giving rise to diverse and bizarre responses.

The reactions of a neurosis thus initiated may be general or local. In the case of mucous colitis they tend to localize in the colon, although general symptoms may also be present.

To help understand why the colon is so often involved in a neurosis, Weiss and English (5) point out that there exists the psychiatric principle of organ language or symbolism of symptoms which hypothesizes that if an outlet cannot be found for emotional tension, then the body will find a means of expressing this tension through a kind of organ language; further the gastrointestinal tract is above all the pathway through which emotions are most often expressed in behavior.

Thus it is, that because the gastrointestinal tract is the oldest system in the body phylogenetically it is most likely to be used to express those emotions which cannot be conveyed through regular channels. However good the intentions of the gastrointestinal tract are, it is foredoomed to failure, since it was never intended to perform these functions. Its misguided efforts to be of service for psychologic purposes results only in dysfunction of the viscera with resultant discomfort to the patients.

Certain etiologic factors which operate often in other diseases seem to have little influence in the causation of this disease. Thus diet has little importance as an etiologic factor, likewise nutrition or vitamin metabolism. It is not a disease of malnutrition since it occurs more frequently among the well to do rather than the clinic patients. Allergy has sometimes been considered to play an important role since it tends to resemble mucous colitis in its protean symptomatology and because the two syndromes tend to occur in the same type of persons. There are undoubtedly some persons with mucous colitis who are hypersensitive to certain foods and who react adversely when they ingest them.

This however is of little therapeutic help since the removal of the offending foodstuffs does not clear up the mucous colitis. Another factor which speaks against allergy as an important etiologic factor is the almost total absence of an eosinophilia which would be expected, if mucous colitis was an asthma-like reaction of the colon. Allergy certainly is not a major etiologic factor in the causation of mucous colitis.

SYMPTOMS

Da Costa (6) was one of the first of the modern clinicians to give an adequate description of mucous colitis, although Osler states that the disease had been recognized for several centuries.

The symptoms manifested by the patient with mucous colitis generally are centered in the abdomen, although at times they are constitutional, varied and bizarre.

Since the patient frequently considers the presence of mucus in the stools the outstanding symptom of his disease, it logically merits first consideration. Mucus in the stool occurs in practically all patients with mucous colitis. Indeed the writer finds it difficult to establish a diagnosis without the presence of mucus in the stools.

Mucus in the stool is in itself not a sign of disease, since the colon normally secretes mucus; indeed it is the only important secretory function possessed by the large bowel. It is only when the secretion of mucus becomes excessive that a pathologic state may be said to exist. This occurs whenever the colon becomes unduly irritated from any of several causes, as from an imbalance of the autonomic nervous system, from the presence of hard feces in the pelvic and rectal colons, from the excessive use of laxatives and purgatives, from water or other enemas, glycerine suppositories and other irritants.

When mucus is present in the stools in excessive amounts, it may appear in moulds, shreds or casts of the intestine, sometimes suggesting to the patient the passing of the lining of the intestine, or of tapeworms.

One of the common causes of excess mucus in the stools other than neurogenic factors is the injudicious use of water enemas or colon irrigations. The recent trend of some non-medical practitioners to exploit colon irrigations as a cure-all, often results in the secretion of excessive mucus and the production of mucous colitis. It has been demonstrated that while a small amount of water may be taken into the rectum without appreciable injury to the mucous membrane, that large amounts of water, if run through the bowel as an irrigation will often irritate the mucous membrane and cause it to secrete excess mucus. This excess secretion of mucus is a defensive mechanism on the part of the colon in which it seeks to protect itself from the irritating effects of unwarranted douching, by coating its surface with the non-irritating protective mucus. Such logic unfortunately often falls on deaf ears on the non-medical practitioners who exploit the "high colon irrigation" and who glibly explain that although the mucus

was not present in their patient in the first instance, it required the large amount of water to bring it out.

Next to mucus, the most annoying and persistent symptom is abdominal pain which occurs in over seventy per cent of the patients, according to reports by White and Jones (2); Friedenwald, Feldman and Rosenthal (7); Bockus, Bank and Wilkinson (8); and Jordon and Kiefer (9). The pain may be localized or diffuse.

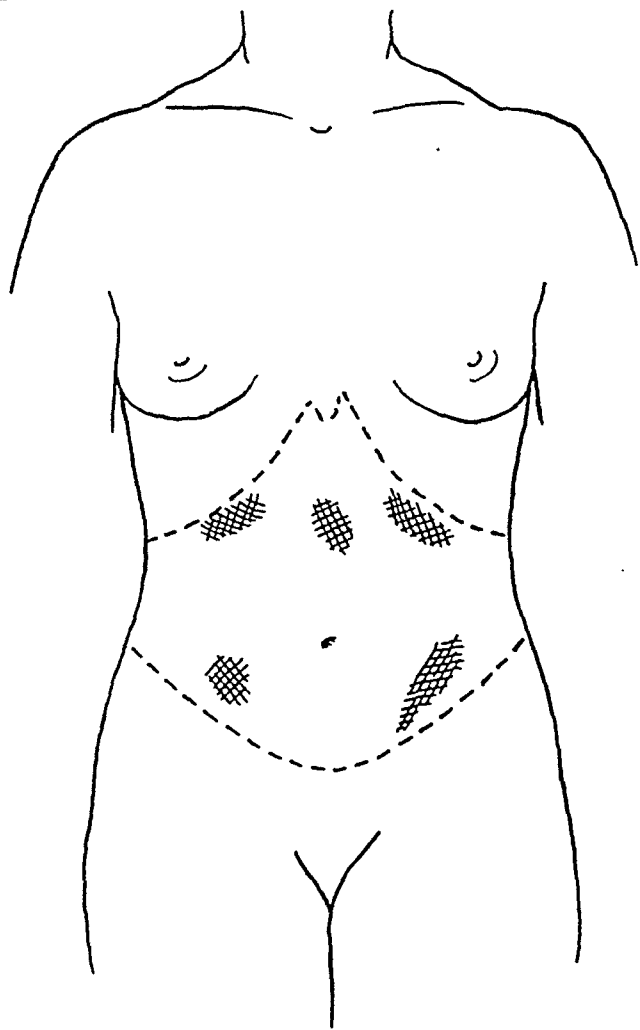


Fig. 1 — Areas of Localized Pain in Mucous Colitis

The left lower quadrant in the approximate region of the descending segment is the commonest region. Other locations are the left costal margin, the epigastrium, the right costal margin, the caecal region. It is these localized areas of pain which give rise to errors in diagnoses, causing mucous colitis to be mistaken for chronic appendicitis, chronic cholecystitis, peptic ulcer and other disturbances of the upper abdomen.

Localized pain occurs most commonly in the left lower quadrant of the abdomen approximately over the descending colon. Other areas for localized pain are the left costal margin, the epigastrium, the right costal margin and the caecum. The areas of localized pain may be present either single or multiple. These localized areas represent referred pain areas from spastic segments of the colon. The pain in these areas commonly has a dull burning quality not unlike heartburn. It may be constant or intermittent and may occur several hours after food taking. Hyperacidity and epigastric heartburn may be associated with it.

These areas of localized pain frequently give rise to errors in diagnosis. It is easily seen that pain in the caecal region will suggest chronic appendicitis, that pain under the right costal margin will suggest chronic cholecystitis and that pain in the epigastrium will suggest peptic ulcer. Indeed White and Jones (2) state that mucous colitis is probably responsible for the removal of more undiseased appendices than any other cause. Eggleston (3) states that twenty-two per cent of his patients with spastic colon and mucous colitis had been subjected to appendectomy and five per cent to cholecystectomy with little improvement. Tumen (10) states that in his study of a large series of patients in whom an incorrect diagnosis of chronic gall bladder disease had been made, in more than half the actual cause of the symptoms was an irritable colon. White and Jones further state that in their series of sixty patients with mucous colitis, that three per cent had had an initial diagnosis of peptic ulcer while an additional three per cent had had an initial diagnosis of gastric carcinoma. In all thirty-one per cent of their patients had needless surgery. White, Cobb and Jones (11) state that in their study the commonest misdiagnosis was gall bladder disease, with peptic ulcer, genitourinary infection and appendicitis not far behind.

The pain is not always localized. At times it is diffuse and may involve the lower half of the abdomen or the upper half or any segment of it. Sometimes there is tenesmus on defecation.

Another annoying symptom is constipation. Many of these people simply do not have a normal stool for months or years at a time. The stools are small, hard, spheroid, constricted or rabbit-like pellets, sometimes like a lead pencil. The stools are often difficult to pass and frequently accompanied by tenesmus or rectal spasm, sometimes by abdominal cramps. Sometimes defecation is followed by distinct pain in the abdomen. From time to time there occurs a discharge of mucus which is often attended by pain of varying degrees of severity and often followed by a feeling of rawness or soreness which may persist for some time.

Occasionally the patient will develop diarrhea which may last for several days to be followed in turn by another period of constipation.

Sometimes the urge to defecate is lost and the patient seems to feel better if there is no defecation. However, this feeling of well being is misleading, and at the best, only temporary, since it is soon followed by gaseous distention from fecal decomposition which soon demands relief. Patients often remark that if they could only get rid of the gas they would not mind the constipation. Unfortunately for them, the problem is not quite so simple, for the cure of the gas distress is inherent in the treatment of the underlying mucous colitis.

Some patients seem to obtain a satisfactory elimination only with the help of laxatives or cathartics, and they soon become addicted to these, since they seem to be unable to obtain a satisfactory elimination without them.

Excessive flatulence and intestinal distention is an-

other frequent symptom. The excessive flatulence has several underlying causes. First is the mechanical factor which results from the spasticity and incidental reduced lumen of the colon. The lumen of the colon in mucous colitis is often a fourth or a fifth of the normal colon. This is so well demonstrated by the barium meal at twenty-four hours, which shows the string-sign which is indicative of the markedly diminished lumen of the colon. The diminished lumen affords a smaller channel for the escape of the formed gases; further as a result of the constipation, the lumen is often still further blocked by the presence of feces. Then there is the chemical factor which results from the changes in the mucous membranes which have lost some of their absorbing power to remove the gases formed in the colon. In health much of the formed intestinal gases, represented by the absorbable fraction, is excreted through the pulmonary system via the blood circulation. Finally, as a result of the constipation and stasis within the colon, decomposition of the stool results with the liberation of additional gases, thereby actually increasing the total volume of formed gases.

Abdominal consciousness is frequently present. In contradistinction to the healthy person, who gives little thought to his abdomen except when he is hungry or when his attention has been drawn to it by a distended bladder or colon, the sufferer from mucous colitis is abdominally conscious much of the time. His abdomen holds an important place in his daily thought life. He is introspective and analytical, he seeks to interpret the various expressions of his abdominal symptoms and seemingly enjoys the recital of them to his physician or any other willing listener. As time goes on, his attention becomes centered more and more in his abdomen and eventually his world of interest comes to center in his abdomen.

Other symptoms which may appear during the course of the disease are nausea, loss of appetite, coated tongue, offensive breath, numerous food intolerances of which milk seems to be a common offender; general debility and irritability, tensional headaches, insomnia, chronic fatigue, and low blood pressure; the skin is often sensitive and manifests vasomotor instability and dermatographia. Some patients develop cardiac symptoms, particularly palpitation, tachycardia, dizziness and faintness. The stigmata of an unstable nervous system may be present as flushing of the skin, sweating, cold and hot hands, irregular pulse, dilated pupils, exaggerated reflexes, mental depression, etc.

Upon physical examination, the patient as a rule is not acutely ill, but commonly manifests the high tensional state. He is anxious, restless, markedly alert to the discussion relative to his case, he is introspective and self analytical. He will talk quite at length about his distressing symptoms and apparently enjoys the recital of the bizarre symptomatology.

After listening to an elongated history the physical examination is disappointing, certainly the objective signs are minimal. The principal sign occurs in the abdomen where the descending colon is usually found to be spastic, palpable and tender with a rope-like con-

sistency. Sometimes there is tenderness in the caecal area.

Other signs are offensive breath, coated tongue, secondary anemia and low blood pressure. There are no specific diagnostic laboratory findings. The urine and blood are frequently normal although the blood may show a mild secondary anemia.

X-ray examination of the gastrointestinal tract shows marked functional disturbances in the colon. There is marked irritability and spasticity of all or any segment of the colon although the descending segment is generally involved. Kantor (12) has called attention that the barium meal often travels faster than is normally the case, the head of the barium meal often reaching the splenic flexure in six hours instead of in nine. The distal portion of the colon is usually markedly spastic and constricted, causing the barium column to assume a stringy or ropy appearance which has been described by Crane (13) as the string sign of mucous colitis.

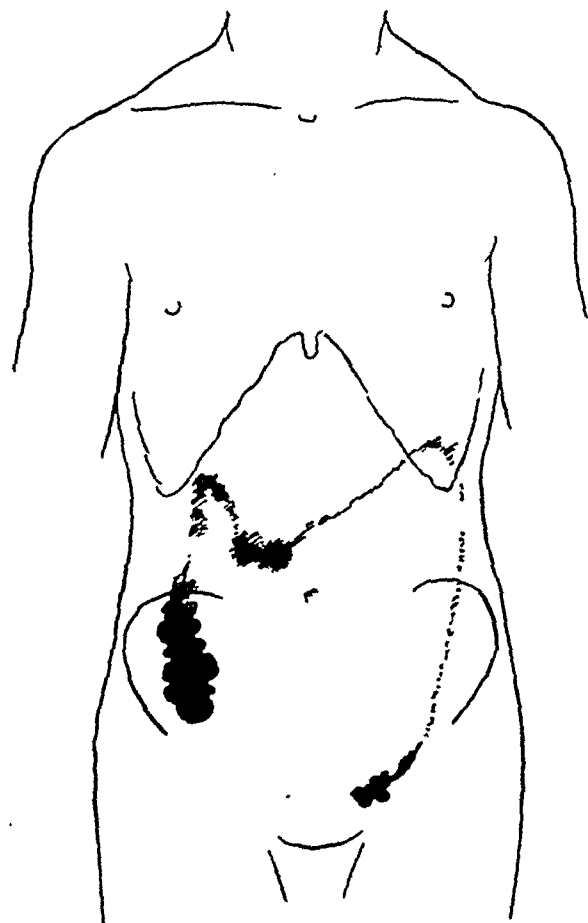


Fig. 2 — X-ray of the colon in mucous colitis at 24 hours showing the string sign.

The sigmoidoscopic examinations have been adequately described by Friedenwald, Feldman and Rosenthal (7) who state that there are three characteristic stages which appear in the course of the disease. In the first stage, the blood vessels are engorged with dilatation of the mucosal capillaries. The mucous mem-

brane is covered with glairy mucus. Slight granularity lending "shad-roë" appearance. In stage two, there is a "generalized injection against which vessels no longer stand out clearly. Surface drier with no glare. Disappearance of light reflex. Mucus dry and tenuous, appearing in patches on mucosal surface." In stage three, the "mucous membrane is thinned out, pale covered with mucus. Pin point ulcerations on removal of surface mucus."

CASE REPORTS

CASE I.

Mrs. E. D., a housewife of 45 years, complained of failing health three months in duration. She had lost her appetite, was feeling tired and worn out and nervous. Her abdomen hurt. She had diffuse abdominal pains which sometimes localized in the epigastrium, and which were burning in character. Also she became constipated and had small stringy stools and passed mucus from time to time.

Physical examination showed an adult white female not acutely ill but in a high tensional state. She weighed 115 pounds, was five feet, four inches in height. Her pulse was 92, her temperature was 97, her respiration was 12, her blood pressure was 106/64. Her tongue was coated. Her head otherwise was within normal limits, likewise her heart and lungs were normal. Her abdomen was somewhat retracted and the descending colon was spastic, palpable and tender and rope-like in character. The liver and spleen were not palpable. The uterus was atrophied. The reflexes were present, equal and exaggerated.

The urine was normal, the blood showed a mild secondary anemia, the Ewald test meal at 60 minutes showed a free acid of 40 and a total of 60. The basal metabolic test was plus 3 per cent.

X-ray examination of the gastrointestinal tract showed a ptosed fishhook type stomach without defects. The cap filled well and at six hours the stomach was empty and the barium was in the small intestine and in the colon up to the splenic flexure. At 24 hours the barium meal was in the colon from the caecum to the rectum. The position of the colon was good. The haustrations of the ascending segment were well defined, but almost all of the transverse and descending segments were markedly spastic and contracted presenting the string sign.

Diagnosis: Mucous Colitis.

Life Situation:

Mrs. E. D., a housewife of 45 years, a former school teacher, had married late in life. At present she had given up her vocation and was keeping house in a small cramped apartment. She had little to do and insufficient activities to occupy her time and talents. She was bored with her form of living. Her days were dull and drab while she waited for her husband to return from his work. During the day and much of the night she dreamed and longed for a spot in the country, specifically in Weld County of Colorado, where she had grown up as a care-free girl. There her family had known everybody of importance and they likewise were important in community affairs. When she had graduated from the teachers' college in Greeley, she had decided to make good on her own merits, so she took to teaching grade school. For one reason or another it continued for fifteen years, but always she longed for that spot in the country where she had lived so happily as a girl. Late in life she married a bookkeeper, she gave up her job as a school teacher, went to live with him in the cramped apartment, but always she dreamed of the farm in Weld County. She convinced her husband that farm life was the desirable existence and they awaited the day when their combined savings would be sufficient to purchase their dream farm.

But one day in 1944, her husband was awakened from a sound sleep with a severe pain in the precordium and radiating pains down the left arm. The doctor diagnosed his case as coronary occlusion and solemnly informed him that it would be a long time, perhaps years, before he would be able to do any manual work again.

To the wife this meant that her husband would be unable to turn farmer. It meant a complete frustration of her whole life long dream and cherished ambition. Shortly afterwards she began to fail in health.

It was evident that it was in the colon that the frustration became localized. The colonic dysfunction was the organ response to the conflict with her life situation, and manifested itself in the mucous colitis.

CASE II.

Mr. C. E., age 40, complains of poor health three years in duration. He is tired and nervous and worn out. He has distress in his abdomen with burning under the left costal margin and in the left lower quadrant of the abdomen. The burning distress comes on several hours after eating and is relieved by soda. Sometimes the distress occurs over the entire abdomen. It may be relieved by rest and external heat. He is markedly constipated and passes small caliber hard stools which are frequently covered by mucus. At times he is short of breath and occasionally asthmatic. He sleeps poorly. He is underweight and his appetite is poor.

Physical examination shows a white adult male, 40 years old, five feet, seven inches in height, weighing 124 pounds. His pulse is 88, his temperature is 98, his respiration is 15, his blood pressure is 122/66.

He is not acutely ill, but he seems to be under marked tension. He seems to observe everything about him and his eyes follow every movement of the physician. His eyes, throat, heart, lungs are within normal limits. There are no signs of asthma at the time of the examination. His liver and spleen are not palpable. The descending colon is spastic, palpable, tender and rope-like in character. The genitalia and reflexes are normal.

The urine is normal, the blood shows a mild secondary anemia. The Ewald test meal and basal metabolic test are within normal limits.

X-ray of the stomach shows a marked gastric irritability but no filling defects. Likewise the duodenal cap is irritable but fills well on manipulation. At six hours the stomach is empty, and the barium meal is past the splenic flexure. At 24 hours the meal is in the colon from the caecum to the sigmoid flexure. It is markedly hyper-tonic throughout its entire length, the descending segment is markedly constricted and shows the string sign.

Diagnosis: Mucous Colitis.

Life Situation:

Mr. E. C. assured us that he knew of no apparent reason why he should be nervous or unhappy. He liked his work as a bookkeeper for a large baking company. He was happily married, his domestic life was congenial, financially he was in the clear. He did not drink, gamble, or indulge in clandestine affairs.

On the face of it, there seemed to be no evident reason for a neurosis. However, the writer recalled that often the real reason might be buried in the subconscious as a submerged fear complex, that it might not operate in the open but in the dark submerged mental recesses, yet nevertheless there it might perform its mischief.

So the questioning was continued with the following results. It appeared that about a year previously, shortly before he began to fail in health, he was set upon one day by a bunch of gangsters and beaten within an inch of his life. The timely arrival of the police alone saved him from destruction. On the approach of the police, the gangsters made a quick get-away in a waiting car. Later one of them was apprehended, but was subsequently released on some technicality. However, during

the preliminary examination it developed that it had all been a mistake. The patient had been mistaken for a notorious labor racketeer who had been their intended victim. Our patient just happened to have the misfortune of resembling him and being in the wrong place at the wrong time. It was all a regrettable mistake.

Here was that submerged fear complex that we were looking for, the one that was gnawing away at his mental vitals. For what had happened once could happen again. Our patient was in mortal fear of being caught in another labor war, accidentally or otherwise, for the city he lived in was notorious for its labor wars. His trip west to our city had been a subconscious flight from fear. His fear had localized in the bowel, causing the mucous colitis.

CASE III.

Miss A. L., an attractive school teacher of 25 years, complained of abdominal distress, loss of strength, nervousness, constipation and mucus in the stools one year in duration. Up to a year ago she had enjoyed fairly good health. Then for no apparent reason she began to go down hill. She had lost about fifteen pounds, she tired easily, slept poorly, developed a coated tongue and an offensive breath and lost her appetite. She was unable to concentrate on her work. She developed abdominal distress characterized by a dull ache in the left lower quadrant of the abdomen. She became markedly constipated and had unsatisfactory stools which were infrequent and markedly constricted, sometimes they contained considerable mucus, and on several occasions she passed large mucus molds of the intestine.

Examination showed an adult white young woman, 25 years old, weighing 110 pounds, measuring five feet, three inches in height. Her pulse was 85, her temperature was 98, her respiration was 16, her blood pressure was 102/64. She was not acutely ill, but in a high tension state.

Her tongue was coated, otherwise her head was normal, likewise her throat, chest, heart, lungs were within normal limits. In the abdomen the descending colon was spastic, palpable, tender, and rope-like in character. The reflexes were present, equal and exaggerated.

The urine and blood were within normal limits, likewise the Ewald test meal was within normal limits.

X-ray of the gastrointestinal tract showed an irritable stomach, and a markedly irritable colon showing the string sign in the descending segment.

Diagnosis: Mucous Colitis.

Life Situation:

This patient, like the previous one, stated that she knew of no reason for being nervous and that she was at peace with the world. She liked her job of teaching school, her relations with her principal were pleasant, her sickness and accident insurance were adequate to provide for accidents and old age, she was engaged to a man whom she was in love with; in fact it seemed just as she had stated, that she was at peace with the world.

Once more it required tactful but persistent interrogation to ferret out the submerged fear complex. It developed that our young school teacher was engaged to a young man with whom she was in love, whom she wished to marry, yet whom she was afraid to marry. She was afraid to marry him because of the family skeleton in the closet which might suddenly reach out from its dark recesses, rattle its bones and wreck her happiness. So she worried herself into a state of impaired health because of a hushed up family scandal in which her father had been the principal actor a number of years previously when he had run afoul of the law in the good old prohibition days. She was afraid that her young man, or possibly his mother, who was a straight-laced Puritan, might not like her family background. She was afraid to tell her young man about the skeleton in the closet

and afraid not to tell him. So she stewed around for one year while her health became impaired and the mucus increased in her stools.

It is evident that it is the bowel speaking the medium of organ language that is expressing fear and anxiety, and causing the mucous colitis.

TREATMENT

In considering the treatment of mucous colitis the following principles come in for consideration:

1. The colon of mucous colitis is the focal point of a neurosis,
2. It is in a state of vaso-motor instability,
3. It is hypertonic and irritable,
4. It is a constipated colon and has acquired faulty habits,
5. The individual with mucous colitis is a neurotic individual and "the neurotic individual has partly lost the ability to relax," says Jacobson (14).
6. The colon of mucous colitis is an irritated colon and sometimes an inflamed colon.
7. In mucous colitis, a vicious cycle has been set up in which psychic states as fear, etc., give rise to somatic symptoms as abdominal pain, etc., and these somatic symptoms in turn give rise to psychic states, thus producing an endless procession of reciprocal factors.

From the foregoing, the following principles of treatment seem logical, as we have pointed out elsewhere (4, 15, 16):

1. The vicious cycle of endless reciprocal factors must be attacked at some vulnerable point and broken up.
2. A general psychotherapeutic approach to the problem, attempting to reach the underlying neurosis with attempted therapy along the lines of ventilation, sympathetic listening, adjustment, redirection, reconstruction or sublimation.
3. Reduction of the general irritability of the neurotic patient through attempts at relaxation by such measures as sedation, physical therapy, exercise, a change in the environment, and other therapeutic agents.
4. Local treatment of the colonic dysfunction through attempts at reducing its irritability as well as reducing the physiologic labors imposed upon it through the medium of bland diets, sedation, antispasmodics, protective inert colloids, oral and parenteral medication, etc.

Accordingly we consider the patient as a human being rather than a set of organs whose dysfunction is to be measured by instruments of precision and rearranged to conform to a set standard. We are primarily interested in him as a human being seeking to exist in a world of conflict. We are interested in the general life problems which make up his daily life in his struggle for existence, his loves, desires, ambitions, conflicts, successes, failures, frustrations, submerged fear complexes, anxieties, hidden feeling of guilt, etc. These frequently seem quite unimportant to the patient who would much rather discuss his bowel dysfunction and who is willing to talk endlessly about his abdominal distress. Yet it is in the analysis of his life situation that

the key to his neurosis lies. So the patient is to be encouraged to talk about himself as a person. This may be time consuming, but it pays dividends.

Adults are to be encouraged to discuss their financial and domestic problems, their professional and business affairs. In younger people, conversation is to be directed to family affairs, finances, security, choice of a career, religious conflicts, marriage, love affairs and sexual affairs.

The technique of psychotherapy is largely a personal procedure with the physician. It need not be surrounded with an air of mysticism, since in its essence it is simple and direct. Indeed many successful physicians practice it without consciously being aware of doing so. There are three main basic factors to be followed: 1) the neurotic patient in the first place wants an audience, so the physician must be a good listener; 2) the neurotic feels that he is a neglected person, so the physician in the second place must be sympathetic, and 3) the neurotic in the third place suffers from a feeling of inadequacy or instability, so the physician must present to the patient a firm program about which the patient can build a constructive program of living, which may take on any of several forms, as reconstruction, adjustment, redirection, sublimation, etc.

The patient must be informed that he has mucous colitis and that it is an expression of a frustration, submerged fear complex or other psychic state resulting from the conflict with his environment, and an attempt must be made to seek out its cause. Some patients will resent this and resist having their private affairs pried into. They will argue that it just does not make sense. They came to the physician to be treated for their abdominal complaint and not to have their domestic or financial affairs inquired into. If the patient makes his objections strong enough and effective enough, he is doomed to have his mucous colitis for a long time.

Treatment, however, is not confined to psychotherapy alone. There are other forms of therapy. Bed rest is a well recognized therapeutic procedure. Bed rest helps to put the entire organism into a state of relaxation by reducing the total amount of sensory-motor activity as well as psychic activity. Likewise it reduces the nutritional requirements of the person from 2500 calories of the ambulatory person to 1500 calories of the bed patient, thereby reducing the physiologic burden on the digestive apparatus. The amount of bed rest is a variable factor. About a month will serve its purpose in many patients. Some patients, however, do not respond well to bed rest, as they are not good company for themselves. When left alone with their own thoughts, they tend to feed on their own morbidity. They are better off being up and about.

Other forms of relaxation which may be employed are vacations, change of environment, exercise, golf, fishing, etc., for those for whom these are suited.

Physical therapy is useful in some patients, as diathermy, infra-red light, sun light, local heat, hydrotherapy, etc. These have a soothing and relaxing effect on the abdomen and help to distract the attention of the patient.

The diet usually employed is the so-called bland diet, which is a balanced diet with a minimum of roughage and the removal of those foodstuffs which are known to be irritants to the digestive tract. Copies of this diet may be found in numerous standard textbooks on dietetics, so it need not be repeated here.

Drugs are often employed to considerable advantage, especially early in the course of treatment when it is desirable to control the symptoms, thereby allaying the anxiety of the patient and establishing confidence in the therapeutic program. To this end, the following drugs are useful: the sedatives, as phenobarbital and the bromides; and the anti-spasmodics as atropine and belladonna. The symptomatic treatment is very helpful in giving immediate relief from some of the distressing symptoms, likewise it attacks the vicious cycle of mucous colitis at a vulnerable point, thereby doing much to encourage the patient to have confidence in the therapeutic procedure.

Other medicaments employed include the bland non-irritating vegetable mucilages which are sometimes employed to advantage. These are generally derived from psyllium seed after the removal of the husks, oil, fiber and other irritating materials, leaving the demulcent mucilloid which has the ability to absorb and hold water, thereby providing a soft matrix for bulk for the stools. Such mucilloid gels exert no demonstrable irritation on the mucous membrane of the colon and are useful in aiding in the formation of larger, bulkier stools. The writer has found the following products to embody these principles: Metamucil (Searle), Mucilose Granules (Stearns) and Mucara (Wyeth).

Cathartics and enemas are to be avoided as they tend to aggravate the existing evil by increasing the hypertonicity of the colon. Mineral oil by mouth is likewise to be avoided, as it interferes with digestion, it causes flatulence, it robs the ingested nutriment of its fat soluble vitamins. Oil retention enemas, however, may be employed as they are soothing without being irritating and they assist in evacuation of the stool.

PROGNOSIS

The prognosis of mucous colitis is always guarded. The disease is never fatal, although it may cause the patient to suffer ill health for years at a time, likewise recurrences are common even in the apparently cured.

If the disease is treated solely as an abdominal syndrome, then the patient will probably continue to have his disease with remissions for many years. If on the other hand it is treated as a neurosis, there is a better chance of a cure. But this is not always an easy procedure, as the nervous system of the person with mucous colitis has acquired certain well formed characteristics. Likewise the inherited tendencies of these persons are buried in the remote past of their ancestors who cannot be reached; likewise the nervous system of the neurotic person has partly lost the ability to relax, also it has acquired a vicious cycle and feeds on its own evil. The frustrations and conflicts of the past have produced fears and anxieties which produce psychic states as anxiety, etc., which in turn produce fur-

ther symptoms producing a vicious cycle with a constant procession of reciprocal factors.

Psychotherapy as practiced by the internist may prove a simple process in some patients, while in others it becomes a major procedure beyond his talents. Such patients must be referred to persons specially trained in this work.

Some patients respond satisfactorily to the combined medical and psychotherapeutic procedures, but there are others in whom the vicious cycle of endless reciprocal factors has become so thoroughly ingrained in the patient that they are never broken up, and the patient goes through life complaining of the ever present mucus in the stool and the abdominal pain. Mucous colitis then becomes a troublesome clinical problem. To these patients life is often just one gas attack after another combined with a sensation of feeling "no good." They are the legion who "go the rounds" seeking something in physical comfort that they never quite seem to find.

Commonly they first consult the local physician and when they have exhausted his talents, they go to the cultist, then to the colon irrigation expert, then perhaps to the faith healer, and when they have sampled all the varieties of the local healing arts, they are apt to visit the big clinic in the distant city, where they are given a thorough overhauling following which they are informed of their diagnosis which they are already quite familiar with. Then they are apt to return to the local physician where they start the cycle all over again. Sometimes instead of wandering, they cling to their local physician with a persistent tenacity consuming excessive amounts of his time and patience with their seemingly endless recital of symptoms resulting from an introspective mental mechanism focused on the deranged colon. A variant of this "going the rounds" seen in congested cities is going from interne to resident to attending physician and after a few months when the service changes is starting the cycle all over again.

Yet it is the duty of the physician to aid and assist these uncomfortable mortals in their search for physical comfort to the limits of his ability. But to do so he must understand them and their problems. It is important that he understand the etiology, pathology and symptomatology of their clinical syndrome; but it is more important that he understand the sufferers them-

selves as human beings living in a complex world trying to pit their wits against the conflicts of a seemingly harsh world and reacting to their frustrations by centering their attentions on the derangements of their colon.

SUMMARY

The present trend is to consider mucous colitis a neurosis of the colon, a form of psychosomatic disease in which the life conflict of the person has been mediated through the sympathetic nervous system to become localized in the colon.

Mucous colitis is definitely associated with psychoneurotic states as high tension states, anxiety states, submerged fear complexes, etc.

The causes of a neurosis are manifold, complicated and prolonged in their genesis. It is seldom that a single factor produces a neurosis, although it may appear to do so.

The gastrointestinal tract is the most likely organ which is used to express a neurosis; however, its good intentions are foredoomed to failure, as it was never intended to perform these functions. Its misguided efforts result in dysfunction of the viscera.

The common symptoms of mucous colitis are mucus in the stools, localized or diffuse abdominal pain, constipation, flatulence; also numerous other local and constitutional symptoms.

The principle physical sign is the presence of spastic, palpable and tender descending colon of rope-like characteristics.

The principal x-ray sign is the string sign which usually occurs in the descending segment of the colon.

In considering treatment, it must be borne in mind that the patient has developed a vicious cycle in which psychic states give rise to somatic symptoms and these in turn to psychic states producing an endless procession of reciprocal factors. This vicious cycle must be attacked and broken up at some vulnerable point.

Among the therapeutic procedures employed are: psychotherapy, bed rest, relaxation, bland diets, sedatives, anti-spasmodics, physical therapy, demulcent gels.

The prognosis is always guarded. The disease is never fatal, cures are sometimes obtained, recurrences are frequent; however, it is apt to be chronic and exist for years at a time.

REFERENCES

1. Hurst, Arthur: Mucous Colitis and Mucous Colic, Chapter XXXIV in *Portis' Diseases of the Digestive System*, Lea and Febiger, Philadelphia, 1941.
2. White, B. V. and Jones, C. M.: Mucous Colitis, *Ann. Int. Med.*, 14:854, 1928.
3. Eggleston, E. L.: Colitis, The Spastic Type. *Jour. Amer. Med. Assoc.*, 91:2049, 1928.
4. Gauss, Harry: The Neurotic Patient. *Amer. Jour. Dig. Dis.*, 11:248, 1944.
5. Weiss and English, O. S.: *Psychosomatic Medicine*, W. B. Saunders Company, Philadelphia, 1943.
6. Da Costa, J. M.: Mucous Enteritis. *Amer. Jour. Med. Sc.*, 89:321, 1871.
7. Friedenwald, J., Feldman, M. and Rosenthal, L. J.: Mucous Colitis; Observations in 500 Cases. *Ann. Int. Med.*, 3:521, 1929.
8. Bockus, H. L., Band and Wilkinson, S. A.: Neurogenic Mucous Colitis. *Amer. Jour. Med. Sc.*, 176:813, 1928.
9. Jordan, S. M. and Kiefer, E. D.: The Irritable Colon. *Jour. Amer. Med. Assoc.*, 93:592, 1929.
10. Tumen, Henry: Treatment of the Patient with Irritable Colon. *Northwest Med.*, 41:42, 1942.
11. White, B. V., Cobb, S. and Jones, C. M.: Mucous Colitis. *Psychom. Med. Monograph* 1, 1939.
12. Kantor, J. L.: Colon Studies. IV. The Roentgen Diagnosis of Colitis. *Amer. Jour. Roentg.*, 17:403, 1927.
13. Crane, A. W.: A Roentgen Sign of Mucous Colitis. *Amer. Jour. Roentg.*, 17:416, 1927.
14. Jacobson, E.: Reduction of Nervous Irritability and Excitement by Progressive Relaxation. *Trans. Sect. Nerv. and Ment., Amer. Med. Assoc.*, 1920.
15. Jordan, Harry: The Spastic Colon. *Ann. Int. Med.*, 3:1128, 1930.
16. Gauss, Harry: Nervous Indigestion. *Colorado Med.*, 29:202, 1932.

An Outline for the Treatment of Peptic Ulcer

By

EARL P. LASHER, JR., M.D., F.A.C.S.

SEATTLE, WASH.

THE PATHOLOGIC ENTITIES of benign gastric and duodenal ulceration have been known for a little over a hundred years. A good historical account of early descriptions is given by Robertson and Hargis (52). It is apparent from recent writings (23, 33) that the disease is becoming more common.

Until recently no attempt at standardization of treatment was apparent, and the older literature therefore is confusing and difficult to evaluate. During the last ten years in this country, and for a longer period abroad, there has been gained sufficient agreement in the general principles of therapy to eliminate many of the less sound methods. Also, enough time has now elapsed and adequate follow-up become sufficiently popular to make material available for study.

This review is presented to clarify the problems of classification of the types of peptic ulcer, so that:

1. A proper method of therapy may be chosen in any single instance.
2. A more accurate prognosis may be offered to the patient.
3. A plan of treatment may be evolved, so that at the end of another ten year period valuable information will be at hand.
4. The age of the patient will be given more consideration.
5. The differences between the diseases 'gastric ulcer' and 'duodenal ulcer' will be appreciated.
6. The anatomic position of the lesion will assume its rightful importance when therapy is selected.

Early in the study of peptic ulcer it was noted that the disease characteristically appeared in young people of a 'tense' emotional type. Wolf and Wolff (66, 67) have convincingly shown the etiologic and therapeutic importance of emotions and personality in lesions of the stomach. Also, it has been known for some time that the total gastric secretion and gastric acidity are increased in patients with peptic ulcer. In our present state of knowledge all rational treatment is founded on a realization of these two facts (53).

Though the tone of the succeeding paragraphs is didactic it is realized that no fast rules can be set and that the art of medicine and surgery cannot be reduced to a formula. In different men's hands the number of patients in any of the groups will vary.

GROUP I

Uncomplicated Gastric or Duodenal Ulcer

TYPE A: In this are placed those patients under

forty with gastric or duodenal ulcer, who consult the physician within six months of the onset of their symptoms, and whose troubles have been limited to 'indigestion,' pain and occasional vomiting. If properly treated these persons have the greatest opportunity to obtain a lasting cure of their disease.

The usual case history is expanded to include inquiry into their emotional difficulties. Troubles in their home or work are corrected whenever possible and every attempt is made to induce a more placid and philosophic outlook toward life. The patient is told that he has a potentially serious and chronic disease, and that his greatest chance for permanent relief is at hand. He must submit to certain studies and a strict regimen of treatment. The lesion is located by means of the barium meal and the gastric acidity determined by gastric analysis with histamine. These data are a necessary baseline. Failure to find evidence of an ulcer in the gastro-intestinal series does not mean that it is not present and, with a proper clinical history, the outline of treatment is not changed (37).

Though some type of compromise is occasionally necessary, every effort is made to have the patient spend two weeks in bed. He must stop smoking (15) and take no alcoholic beverages whatever. For the first few days only hourly milk and cream mixtures are given; and supported by an amphoteric substance and anti-spasmodics as needed. Supplements are added at intervals and a progressive dietary regimen evolved. Sedatives may be necessary. As his activity is gradually increased more effort is expended to reduce the nervous tension. The diet is not allowed to progress beyond six small bland meals per day.

If he becomes free of symptoms the gastro-intestinal series is repeated at the end of three months. Then, if all signs of peptic ulcer are absent, the patient is told that in all likelihood another three months of the restricted regimen will be all that is needed. This advice is modified by the time of the year. Ulcer symptoms are usually cyclic in appearance and tend to recur in the early Spring and in the Fall (46). It is wise, therefore, to hold the patient to his routine until late Spring or Summer whenever possible. After his three-month's study he may be allowed to adopt a schedule of three restricted meals a day, and from this time until he is permitted a normal life he is seen about once a month.

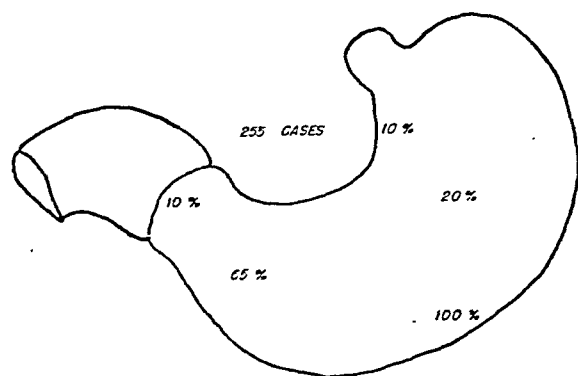
The decision to be made at the sixth month is difficult. The patient is impressed with the fact that his disease is a chronic one, and that relapses are not uncommon, and that he has done well so far and will probably avoid further trouble if he is careful and co-operative. The physician must now judge how much

progress he has made in changing the personality of the individual and thus anticipate how much liberty he may be given. In all instances the patient is told that follow-up visits are necessary.

TYPE B: In this are included those persons under forty, with gastric or duodenal ulcer, who have failed to respond satisfactorily to a good medical regimen observed over three months, but who have, as yet, developed no significant complication of their disease. In many instances the adequacy of the treatment may be questioned; and it is then advisable to re-instruct them in the routine outlined for TYPE A and follow them more closely. Frequently emotional factors have not been released and the help of a psychiatrist is decisive (63).

If failure has been complete the patient is advised of the seriousness of his position and told his prognosis in terms of the medical experience now found in the literature. A continued conservative regimen will benefit about 60% of patients (20, 16, 14), and subject them to a mortality of 3-6% (20, 16). Taking into consideration the degree of excellence of surgery obtainable an operation will help some 85% (20, 26, 30, 38, 50, 54, 62), but carries with it the disadvantages of expense, morbidity and mortality (gastric resection, 2%; gastroenterostomy, $\frac{1}{2}$ -1%) (20, 62, 68) and the hazard of recurrent, post-operative ulcer formation (5-10%) (14, 27, 29, 34, 50). In addition it will not relieve him of the necessity of following a restricted routine. An effort is made to determine how much his illness is costing him under conservative treatment: this includes time lost from work, doctor's bills, loss of recreation and social pleasures and the tax of more or less constant pain. The patient is then allowed to make his own decision.

TYPE C: Within this group are those persons whose ulcer is gastric, and in whom the presence of carcinoma is suspected. The location of the lesion is of great significance (3, 2, 60, Fig. 3), and employing all our available methods, a correct diagnosis can be made in



THE LESION IS CANCER IN THESE LOCATIONS IN THE GIVEN PERCENTAGES
ALLEN - WELCH 1941

FIG. 3

about 95% of instances (20, 21, 2, 60). However, one

is not justified in waiting too long for a questionable response to occur. By and large gastric ulcer is a more serious lesion than duodenal ulcer (9, 20, 26, 43, 47); and, as has been shown by Cooper (8), there is no excuse for the long period of conservative treatment and indecision that precedes the usual operation for gastric cancer. Certainly three weeks of doubt justify an exploration. They do not, however, sustain the decision to operate when the surgeon has the preconceived notion that a resection will be done regardless of his findings. Statistical evidence does not uphold the argument that any gastric ulcer should be resected because of the possibility of carcinoma (20).

If the roentgenologist, or the gastroscopist believes that the ulcer is carcinomatous exploration would seem a wise thing. In the difficult case peritoneoscopy is not often helpful. The gastric analysis, however, when done carefully with histamine, is a very accurate indicator up to the age of 60. In Holman's (21) studies it proved to be the most reliable (history and physical examination 77%, gastro-intestinal series 79%, gastric analysis 91%).

For reasons discussed below as much information as possible is gained before operation and kept in mind when the lesion is exposed at the table.

TYPE D: In this are those patients over forty with duodenal ulcer, either recently acquired or of some years duration. For them the outlook is decidedly different from the group under forty because of the increased likelihood of the appearance of certain of the major complications of the disease, and because of the greatly increased mortality attendant upon them (6, 43, 58) (Figs. 1, 2, 4).

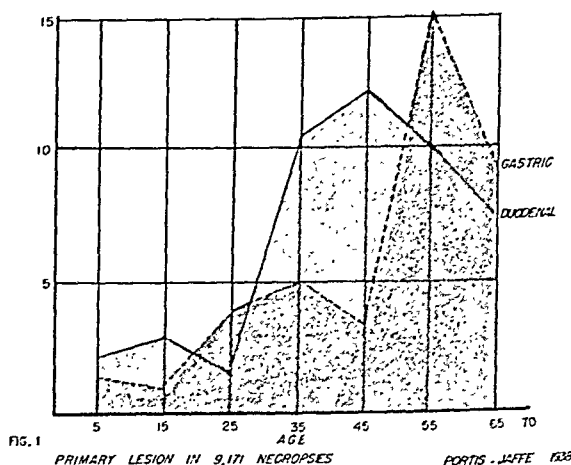


FIG. 1

PRIMARY LESION IN 9,171 NECROPSIES

PORTS - JAFFE 1939

These factors need not influence one to forego a complete medical plan as outlined above, and there is no justification in suggesting operation as the first or only therapeutic method worth trying. If, however, a patient in this group does not respond readily he is advised of the hazards to which he is exposed, and a definite effort is made to induce him to consider operative treatment.

In these individuals the procedure of choice is gastric

resection (20, 31, 50); excising about two-thirds of the stomach, and removing the ulcer-bearing portion of the duodenum, if, in the opinion of the operator, this last is not too dangerous.

TYPE E: This comprises those patients over forty who have a gastric ulcer. In them, one of the first considerations to be dealt with is the possibility of the lesion being either primarily, or, rarely, secondarily cancerous. All in this group are studied as completely as available equipment will permit, and, as suggested in the discussion of **TYPE C**, a rapid response to conservative treatment is required. A decision as to the advisability of operative therapy is not put off more than a month. There are two reasons for this: the first being the fear that the ulcer is carcinomatous, and the second that the dangers of chronic gastric ulcer in a person over 40 are even greater than those of a duodenal ulcer at this time of life (9, 20, 26) (Fig. 1, 2).

carcinoma. In instances of the latter disease a more radical operation, of the Ogilvie type (42), is preferable.

GROUP II

Duodenal Ulcer in which Some Complication is Present

TYPE A: In this the ulcer is at the pylorus and the symptoms and signs of pyloric obstruction are present. Here it is first necessary to determine the degree of spasm that is responsible for the occlusion. This is done by placing the patient at bed rest and restricting the diet as in the early days of the routine for **TYPE A**, **GROUP 1**. Belladonna is used freely and the stomach is emptied night and morning by means of a small Levine tube. Care is taken to prevent alkalosis and hypoproteinemia since edema at the outlet can be as effective a barrier as muscle spasm. As the size of the stomach decreases and the tone of its walls improves there is often a concomitant diminution in the obstruction, and it may disappear entirely. A few weeks spent with this therapeutic trial always precedes any surgical attempt to correct the condition.

When conservative methods have failed a gastro-enterostomy is the operation of choice. This for four reasons: it provides prolonged, effective relief in 90% of the patients (20), it carries a lower mortality rate than does gastric resection, especially in an individual who has been subjected to a long period of starvation: the ulcer causing pyloric obstruction is usually one that is tending to heal and has demonstrated that tendency by the deposition of scar tissue, and, hence, cicatricial contracture about it: the procedure leaves resection for the rare patient in whom a recurrence of activity occurs.

TYPE B: Duodenal Ulcer with Acute Perforation into the Peritoneal Cavity — Fortunately there is little difference of opinion concerning treatment of these patients. The disease presents a surgical emergency. Within the last few years, however, some writers have advocated the execution of a gastric resection at the time of the acute episode (56). This is usually unwise for two reasons: the patient with a perforated ulcer is not in the best general condition to undergo so extensive a procedure; and simple closure of the perforation therefore carries a lower mortality: also 96% of duodenal ulcers that perforate into the peritoneal cavity are on the anterior wall of the first few centimeters of the duodenum (43, 47). The constant movement of the liver over this part of the intestinal tract with each respiration prevents the formation of adhesions as the ulcer is penetrating and therefore prepares the way for a free perforation. Duodenal ulcer in this location is in a fairly advantageous spot. As shown in Figures A and B, it is not close to any of the large vessels and is therefore unlikely to cause significant hemorrhage. Being removed from the pancreas, penetration into it and the resultant intractable pain is not apt to occur (48, 44). The possibilities of pyloric occlusion or a second perforation are thus left as the only complications to be really feared; and, to be consistent in our arguments, neither of these, per se, is a clear indication for gastric resection. Therefore, after simple closure, it is good

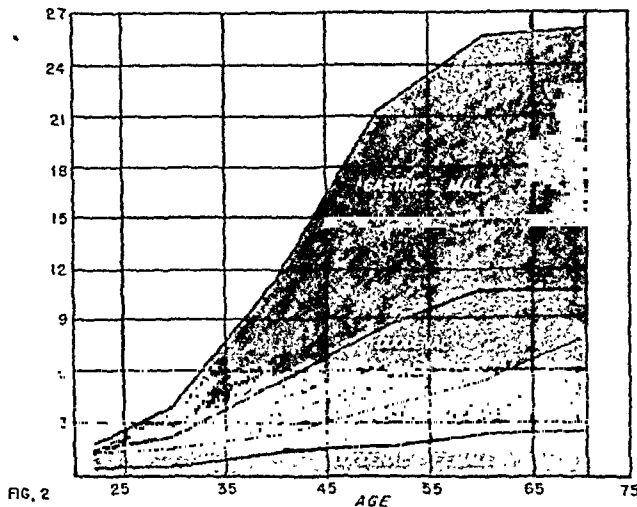


FIG. 2
AVERAGE ANNUAL DEATH RATES PER 100,000
GOWDRI 1931-35

Should an operation seem desirable, it is important that the clinical diagnosis be clear in the surgeon's mind. It is occasionally difficult, with the gross specimen in hand, and even with the aid of a frozen sec-

PERFORATED PEPTIC ULCER

7,564 CASES COLLECTED FROM THE LITERATURE

AVERAGE MORTALITY 27 %

GASTRIC 33.2 %

DUODENAL 21.6 %

AVERAGE MORTALITY OVER 50 YEARS OF AGE 45.9 %

AVERAGE MORTALITY UNDER 50 YEARS OF AGE 19.3 %

PALETTA - HILL 1943

FIG. 4

tion, to differentiate between gastric ulcer and gastric

judgment to allow the patient a trial on a strict medical regimen as given above.

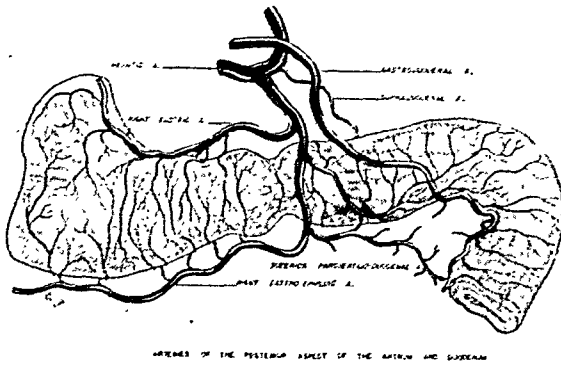


Figure A

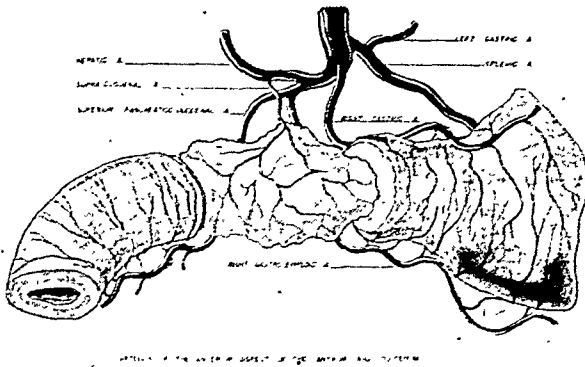


Figure B

TYPE C: Under this heading are included patients under forty with duodenal ulcer in whom hemorrhage has appeared as a complication. In these persons it is necessary to first determine the amount of bleeding (22, 41). Much confusion is apparent in the literature because of failure to do this. Massive hemorrhage might be described as that which is abrupt in onset, usually producing some degree of shock in a few minutes. It reduces the hemoglobin to 50% of normal, or below, when calculated after a state of adequate hydration of the patient has been attained. Because of the anatomy of the region (49, Fig. A and B), such bleeding almost always arises from ulceration along the lesser curvature of the stomach or in the posterior portion of the first ten centimeters of the duodenum. Erosion of a large vessel, such as the gastro-duodenal, superior pancreatico-duodenal or one of their primary branches is needed to provide the volume of blood that is so rapidly lost.

Hemorrhage of a lesser degree may arise from an ulcer in almost any location.

Either type of bleeding in people of this age rarely causes death (2-4%; 6, 10, 22), and as a general rule, conservative treatment is advised. Where bleeding is copious, no strenuous effort is made to raise the blood pressure rapidly, and the patient is given nothing by

mouth for forty-eight hours after the bleeding has stopped. The progressive Sippy routine is then begun and bed rest continued for about ten days. No roentgenologic studies are attempted for at least two weeks after the hemorrhage. This is a distinct disadvantage because by that time sufficient healing may have been induced so that an ulcer in the posterior position cannot be visualized. X-ray studies are necessary, however, to eliminate the possibility that a gastric ulcer or some more unusual lesion was the source of the hemorrhage (51).

In instances where bleeding is not copious some type of bland diet is started at once (41), and the effects of the blood loss corrected by transfusion and the administration of an iron preparation such as ferrous gluconate, which is not irritating and is easily assimilated.

As a rule, patients in this group are instructed much as are those classified under GROUP I, TYPE B, in whom the response to a good medical regimen was poor. If the hemorrhage occurred during a period of adequate treatment, or if it was an episode in an individual in whom the disease was manifestly uncontrolled, surgical therapy is urged. The operation of choice is gastric resection, and in all cases where bleeding is a significant complication a most earnest attempt is made to remove the ulcer-bearing part of the duodenum.

TYPE D: In this are placed the unfortunate victims of duodenal ulcer who have not obtained significant benefit from any method of treatment now known. Many have been subjected to one or more surgical procedures.

Most of these patients are constitutionally inferior or are periodic or habitual alcoholics, or present a family background of gastric disease. This last may suggest some inherited factor in the cause of the lesion; or it may be the result of years of bad dietary habits and poor food. Many are indigent and constantly harassed by worry, starvation and repeated illnesses.

Here some type of financial aid or other tangible assistance is a necessity. Unless a permanent change is effected in the patient's habits and circumstances, no purely medical or surgical plan can be expected to succeed.

It is within this group, where there is so little else to offer and where the outlook is dark, that trials of new methods such as a continuous neutralizing drip (64, 65), enterogastrone (24), or intrathoracic division of the two vagi are made (12, 13). When success can be attained here the method can be applied to others with peptic ulcer with real optimism.

GROUP III

Massive Hemorrhage from Peptic Ulcer after the Age of Forty

In this are grouped the patients over 40 who suffer hemorrhage from either gastric or duodenal ulceration. Again, the amount of bleeding is of great importance. When of only slight degree, the individual is advised as he would be were he a younger man with a larger hemorrhage: GROUP II, TYPE C.

Massive hemorrhage from a peptic ulcer in a person

over forty is a very serious event (6, 10, 19, 20, 22, 36, 58, 65). At the present time about 25% of these patients die; and half-hearted surgical measures serve only to increase the mortality. Recent figures indicate that an early evaluation of the case is essential, and that a decision to intervene or to pursue a conservative plan is necessary within the first forty-eight hours.

Where several liters of blood are available and efficient help and good nursing attention can be obtained gastric resection, removing the ulcer, under local anesthesia, is the procedure of choice. By this means the bleeding can be effectively and permanently stopped quickly. It is then necessary, however, to exert considerable effort supporting the individual in whom a major operation was done at an inopportune time (17, 18, 19, 20, 22).

When surgical treatment is rejected this decision becomes final after the second day and is not changed until the patient has improved sufficiently to undergo a resection as an elective operation. It is unfair to the patient and to the surgeon to change plans when a second hemorrhage occurs before the effects of the first have been corrected (28, 36, 41, 65).

When the patient over forty who has suffered massive bleeding from a gastric or duodenal ulcer has recovered he is urged to have a gastric resection without undue delay.

GROUP IV

Gastric Ulcer in which Some Complication is Present

TYPE A: In this are those patients in whom acute perforation of a gastric ulcer has occurred. The problems presented here are greater than in instances of acute perforation of a duodenal ulcer. Not infrequently the posterior gastric wall has been the site of the penetration and drainage has been into the lesser peritoneal sac. Diagnosis is difficult and the interval before considering surgical attention often prolonged. The patient is usually in an older age group and therefore in a more precarious position. Also the possibility of the ulcer being carcinomatous is worthy of consideration. It is thus wise to be prepared to do an extensive operative procedure at the time the lesion is attacked. With the sulfonamides, penicillin, and blood available simple closure of a perforation in cancerous tissue is more hazardous than gastric resection (5).

Where simple closure of a perforated benign ulcer is done the patient is advised as was the individual with a perforated duodenal ulcer. However, since a gastric ulcer is usually close to large vessels along the lesser curvature, failure to respond to medical treatment within three months suggests the advisability of considering gastric resection.

TYPE B: In this are the persons with gastric ulcer complicated by hemorrhage. Due to the anatomy of the part involved and the higher mortality found in instances of hemorrhage from gastric ulcer the decisions noted under GROUP III are maintained regardless of the amount of bleeding exhibited.

TYPE C: This is reserved for the group of patients with chronic or recurring gastric ulcer in whom the de-

velopment of carcinoma of the stomach is feared or suspected. In general the considerations advanced under GROUP I, TYPE C are held. It is probable that only about 5% of benign gastric ulcers become inalignant (2, 60, 61).

TYPE D: In this are the patients with long-standing or recurring gastric ulcer. It has been noted that gastric ulcer, unlike duodenal ulcer, may heal fairly rapidly but reappear in the same or an adjacent region (45, 55, 67). Also, statistics indicate that gastric resection for gastric ulcer offers somewhat better immediate and long-term results than for duodenal ulcer (20). It is reasonable, therefore, to seriously consider the advisability of gastric resection in patients with chronic or recurring gastric ulcer.

GROUP V

Marginal or Recurrent or Jejunal Ulcer and Their Complications

In these patients no general rules apply. Each problem may be so complex that it is futile to attempt generalizations beyond noting that the disease occurs in 5-10% of all patients who undergo gastroenterostomy or gastric resection for peptic ulcer (1, 4, 27, 34, 39, 59); that hemorrhage, and perforation, either free, or into an adjacent viscus are not uncommon complications; and that, if surgical treatment is elected, better results follow gastric resection, after the dismantling of the enterostomy and resection of the ulcer-bearing portion of the bowel, than any other method (1, 20, 29).

Though many of these individuals are of the type mentioned above in considering intractable duodenal ulcer (GROUP II, TYPE D), something can be done prophylactically to prevent the appearance of jejunal ulcer and to reduce the incidence of hemorrhage as a complication. The lower the part of the intestinal tract that is exposed to the gastric secretions the more likely is ulceration to appear (31, 32). It is unwise, therefore, to use a long proximal loop as was advocated some years ago when an anterior type of anastomosis was done routinely. When the transverse mesocolon is of normal length a posterior anastomosis with a short proximal loop is a better procedure. Where the mesocolon is short an anterior type with a short loop is safer and preferable.

Though the frequency of massive hemorrhage, and of gastrojejunal fistula is reduced by placing the anastomosis well away from the colon and the main stem and arcades of the middle colic artery it is wise to use judgment in this since any secondary procedure requiring mobilization of a deeply placed anastomosis is technically difficult.

Recently one writer has advocated a return to the classical Polya type of operation in preference to the Hofmeister modification in which the lesser curvature side of the anastomosis is sealed for a short distance. His (50) desire in doing this is to increase the amount of alkaline duodenal content that is poured into the stomach and thus reduce the chance of recurrent gastric ulceration. This argument is not without fault. Re-

current or "marginal" ulceration is almost always within the distal jejunal loop (34, 39), and it would therefore seem better to have the highest possible pH here and to rely on the actual resection of acid-secreting mucosa to reduce the gastric acidity.

GROUP VI

Peptic Ulcer of the Esophagus

Fortunately this malady is uncommon (7, 11, 25). It usually responds to treatment without operative intervention other than esophagoscopy and bouginage. But there are at least two types. In the first the etiology is unknown, as in peptic ulcer elsewhere. Other patients show evidence of a short esophagus, diaphragmatic hernia, or incompetent cardia with presumed regurgitation of gastric secretion into the lower esophagus and abnormal retention of it there. In these instances surgical correction of an underlying defect may be necessary before a lasting cure can be obtained by other means.

Perhaps the most important procedure in patients with an ulcer of the esophagus is accurate diagnosis by means of the barium swallow, and by esophagoscopy and biopsy so that the occasional person with esophageal carcinoma, in whom the appearance of pain precedes obstructive symptoms, is found and subjected to the proper surgical treatment.

GROUP VII

Gastroduodenal Ulceration in the Aged

It is becoming increasingly apparent that gastric or duodenal ulceration may appear for the first time in elderly individuals (35, 40). In many reports these patients are included with the younger people with peptic ulcer. They should not be as there are fundamental differences in the two diseases. Gastroduodenal ulcerations of the aged are often multiple, more frequently gastric than duodenal, almost as common in women as in men, and their appearance is only rarely associated with gastric hyperacidity. Within the stomach they are often scattered high on the posterior wall, well away from the "magenstrasse."

Though little is known of the usual course of the disease it is likely that it is dangerous, especially because of the common occurrence of exsanguinating hemorrhage as a complication. Circulatory disturbances secondary to arteriosclerosis are probably responsible for the appearance of the lesions and their alarming consequences.

Little is expected from surgical treatment (57). The vascular changes are widespread and there is no hyperacidity to combat, and the patients are usually in poor physical condition.

DISCUSSION

Thoughts on peptic ulcer are changing. And the disease embraces so many clinical syndromes that it is unlikely that any one procedure or type of therapy will be found universally efficacious. At the present time the causes of the lesions are not known (53), and, though there has been a great wave of enthusiasm among surgeons, resection of the stomach does not seem the therapeutic ultimate that is desired; nor is it probable that its wider use has decreased the mortality from the disease. Though several writers tabulate the mortalities of the complications of the ulcer according to age, none does the same for gastric resection at various periods of life. The figures for almost any operation can be improved by using it predominantly in young people. Temporarily the morbidity has been diminished in many instances and this is certainly beneficial. It does not justify advising certain patients with gastric or duodenal ulcer that a cure can be obtained.

SUMMARY

The following classification of patients with peptic ulcer is given and indications for treatment in each instance discussed.

GROUP I: Uncomplicated Gastric or Duodenal Ulcer

- Type A: New ulcer, young person.
- Type B: Recurrent ulcer, young person.
- Type C: Gastric ulcer, question of carcinoma.
- Type D: Duodenal ulcer, over forty years of age.
- Type E: Gastric ulcer, over forty years of age.

GROUP II: Duodenal Ulcer in which Some Complication is Present

- Type A: Pyloric Obstruction.
- Type B: Acute Perforation.
- Type C: Hemorrhage, under forty years of age.
- Type D: Intractable Ulcer.

GROUP III: Massive Hemorrhage from Gastric or Duodenal Ulcer After the Age of Forty

GROUP IV: Gastric Ulcer in which Some Complication is Present

- Type A: Acute Perforation.
- Type B: Hemorrhage, at any age.
- Type C: Carcinoma.
- Type D: Chronic or Recurring Gastric Ulcer.

GROUP V: Marginal or Jejunal Ulcer and Its Complications

GROUP VI: Peptic Ulcer of the Esophagus

GROUP VII: Gastroduodenal Ulceration of the Aged

REFERENCES

1. Allen, A. W.: An Aseptic Technic Applicable to Gastrojejunal Colic Fistula. *Surgery*, 1:338, 1937.
2. Allen, A. W.: Gastric Ulcer and Cancer. *Surgery*, 17:750, 1945.
3. Allen, A. W. and Welch, C.: Gastric Ulcer; Significance of this Diagnosis and its Relationship to Cancer. *Ann. Surg.*, 114:498, 1941.
4. Atwater, J. S., Butt, H. R. and Priestley, J. T.: Gastrojejunal Colic Fistulae: with Special Reference to Associated Nutritional Deficiencies and Certain Surgical Aspects. *Ann. Surg.*, 117:414, 1943.
5. Bisgard, J. D. and Overmiller, W.: Emergency Gastrectomy for Acute Perforation of Carcinoma of the Stomach, with Diffuse

- Soiling of the Free Peritoneal Cavity. *Ann. Surg.*, 120:526, 1944.
6. Blackford, J. M. and Cole, W. S.: Massive Hemorrhage from Peptic Ulcer. A Study Based on the Vital Statistics of the City of Seattle. *Am. J. Dig. Dis.*, 6:637, 1939.
7. Cleaver, E. E.: Chronic Peptic Ulceration of the Esophagus. *Am. J. Dig. Dis.*, 10:319, 1943.
8. Cooper, W. A.: The Problem of Gastric Cancer. *J. A. M. A.*, 116:2125, 1941.
9. Cowdry, E. V.: Problems in Ageing. Williams and Wilkins, Baltimore, 1942.
10. Crohn, B. B. and Lerner, H. H.: Gross Hemorrhage as a Complication of Peptic Ulcer. *Am. J. Dig. Dis.*, 6:15, 1939.
11. Dick, R. C. and Hurst, A.: Peptic Ulcer of the Esophagus. *Quart. J. Med. (New Series)*, 11:105, 1942.
12. Dragstedt, L. R., Palmer, W. L., Schafer, P. W. and Hodges, P. C.: Supradiaphragmatic Section of Vagus Nerves in Treatment of Duodenal and Gastric Ulcers. *Gastroenterology*, 3:450, 1944.
13. Dragstedt, L. R. and Schafer, P. W.: Removal of Vagus Innervation of the Stomach in Gastroduodenal Ulcer. *Surgery*, 17:742, 1945.
14. Dwyer, M. F., Blackford, J. M., Cole, W. S. and Williams, R. H.: Peptic Ulcer; Review of 1,033 Cases and Follow-Up Study of Patients Diagnosed Between 10 and 20 Years Ago. *Radiology*, 36:217, 1941.
15. Ehrenfeld, I. and Sturtevant, M.: The Effect of Smoking Tobacco on Gastric Acidity. *Am. J. Med. Sci.*, 201:81, 1941.
16. Emery, E. S. and Monroe, R. T.: Peptic Ulcer: Nature and Treatment Based on a Study of One Thousand, Four Hundred and Thirty-Five Cases. *Arch. Int. Med.*, 55:271, 1935.
17. Finsterer, H.: Operative Treatment of Severe Gastric Hemorrhage of Ulcer Origin. *Lancet*, 2:308, 1936.
18. Finsterer, H.: Surgical Treatment of Acute Profuse Gastric Hemorrhages. *S. G. & O.*, 69:291, 1939.
19. Gordon-Taylor, J.: The Attitude of Surgery to Hematemesis. *Lancet*, 2:811, 1935.
20. Heuer, G. J.: The Treatment of Peptic Ulcer. J. B. Lippincott Co., Philadelphia, 1944.
21. Holman, C.: The Diagnosis of Gastric Carcinoma and Peptic Ulcer. *J. A. M. A.*, 108:1383, 1937.
22. Holman, C. W.: Severe Hemorrhage in Gastric and Duodenal Ulcer: A Study of 90 Cases. *Arch. Surg.*, 40:150, 1940.
23. Hurst, A.: Digestive Disorders in Soldiers. *Am. J. Dig. Dis.*, 8:321, 1941.
24. Ivy, A. C.: Prevention of Recurrence of "Peptic Ulcer": Experimental Study. *Gastroenterology*, 3:443, 1944.
25. Jackson, C.: Peptic Ulcer of the Esophagus. *J. A. M. A.*, 92:369, 1929.
26. Judd, E. S. and Priestley, J. T.: The Treatment of Gastric Ulcer. *S. G. & O.*, 77:21, 1943.
27. Kiefer, E. D.: Jejunal Ulcers and Recurrent Hemorrhages after Partial and Subtotal Gastrectomy for Peptic Ulcer. *J. A. M. A.*, 120:814, 1942.
28. Kirsner, J. B. and Palmer, W. L.: Peptic Ulcer: The Treatment of Massive Hemorrhage. *Internat. Clin.*, 4:105, 1939.
29. Lahey, F. H.: Diagnosis and Management of Gastrojejunal Ulcer and Gastrojejunalic Fistula. *Surg. Clin. N. America*, 20:767, (June) 1940.
30. Lahey, F. H.: Indications for Gastric Resection. *Am. J. Dig. Dis.*, 8:180, 1941.
31. Lannin, B. G.: Experimental Evaluation of a Satisfactory Operation for Ulcer. *Surgery*, 17:712, 1945.
32. McMaster, P. E.: Effects of Diverting the Gastric Contents to the Lower Intestinal Levels. *Arch. Surg.*, 28:825, 1934.
33. McKinlay, C. A.: Medical Causes of Rejection in Selective Service Registrants. *Minnesota Med.*, 25:255, 1942.
34. Marshall, S. F.: A Plan for the Surgical Management of Gastrojejunalic Fistula. *Ann. Surg.*, 121:620, 1945.
35. Meyer, J. and Saphir, O.: Peptic Ulcer in the Aged; a Clinical and Post-Mortem Study. *Am. J. Dig. Dis.*, 10:28, 1943.
36. Miller, T. G. and Elsom, K. A.: The Management of Massive Hemorrhage from Peptic Ulcer. *Med. Clin. N. America*, 22:1711, (November) 1938.
37. Miller, T. G.: The Causes of Indigestion and Their Recognition. *New England J. Med.*, 224:537, 1941.
38. Miller, G. G.: Subtotal Gastrectomy for Gastro-Duodenal Ulcer. *Canadian M. A. J.*, 44:570, 1941.
39. Montgomery, M. M. and Kirshbaum, J. D.: Jejunal (Anastomotic) Ulcer. *Arch. Int. Med.*, 67:609, 1941.
40. Muslow, F. W.: Peptic Ulcer of the Aged. *Am. J. Dig. Dis.*, 8:112, 1941.
41. Nicholson, J. T. L. and Miller, T. G.: The Prompt-Feeding Program for Bleeding Gastric and Duodenal Ulcer: A Report on Thirty-Two Cases and an Analysis of 1396 Recorded Cases. *Am. J. Dig. Dis.*, 8:446, 1941.
42. Ogilvie, W. H.: Cancer of the Stomach. *S. G. & O.*, 68:295, 1939.
43. Paletta, F. X. and Hill, W. R.: Acute Perforated Gastric and Duodenal Ulcers. *Surgery*, 14:32, 1943.
44. Palmer, W. L.: The Mechanism of Pain in Gastric and Duodenal Ulcers. I. Achlorhydria. *Arch. Int. Med.*, 38:603, 1926.
45. Palmer, W. L., Schindler, R. and Templeton, F. C.: The Development and Healing of Gastric Ulcer. *Am. J. Dig. Dis.*, 5:501, 1938.
46. Petersen, W. F.: The Patient and the Weather, Vol. II, p. 292. Edwards Bros., Ann Arbor, Mich., 1934-38.
47. Portis, S. A. and Jaffe, R. H.: A Study of Peptic Ulcer Based on Necropsy Records. *J. A. M. A.*, 110:6, 1938.
48. Rabinovich, J., Pines, B. and Teicher, I.: Pathogenesis and Pathologic Changes in Peptic Ulcer; and Production of Pain. *Arch. Int. Med.*, 67:620, 1941.
49. Reeves, T. B.: A Study of the Arteries Supplying the Stomach and Duodenum and Their Relation to Ulcer. *S. G. & O.*, 30:374, 1920.
50. Rienhoff, W. F.: An Analysis of the Results of the Surgical Treatment of 260 Consecutive Cases of Chronic Peptic Ulcer of the Duodenum. *Ann. Surg.*, 121:583, 1945.
51. Rivers, A. B. and Wilbur, D. L.: Intrinsic Gastro-Duodenal Lesions as Causative Factors in Hematemesis. *Arch. Int. Med.*, 50:621, 1932.
52. Robertson, H. E. and Hargis, E. H.: Duodenal Ulcer: An Anatomic Study. *Med. Clin. N. America*, 10:65, (January) 1925.
53. Sanders, L. C.: Etiology of Peptic Ulcer. *Rev. of Gastro-enterology*, 8:1, 1941.
54. Sanders, R. L.: Partial Gastrectomy for Duodenal Ulcer. *South. Surg.*, 9:878, 1940.
55. Schindler, R.: Gastroscopy: The Endoscopic Study of Gastric Pathology. Univ. of Chicago Press, Chicago, 1937.
56. Strauss, A.: Primary Gastric Resection for Perforated Gastro-duodenal Ulcers. *Ann. Surg.*, 120:60, 1944.
57. Tanner, N. C.: Gastro-Duodenal Surgery in the Aged. *Brit. Med. J.*, 1:563, 1943.
58. Thorstad, M. J.: The Problem of the Bleeding Peptic Ulcer — A Review of 284 Patients Admitted to Harper Hospital During the Years 1931-1941. *Surgery*, 12:964, 1942.
59. Walters, W. and Claggett, O. T.: Gastrojejunalic Ulcer and Fistula. *Am. J. Surg.*, 46:94, 1939.
60. Walters, W.: Malignant Gastric Lesions Simulating Benign Lesions. *Proc. Staff Meet. Mayo Clin.*, 15:638, 1940.
61. Walters, W., Gray, H. K., Priestley, J. T., Lewis, E. B. and Berkson, J.: Malignant Lesions of the Stomach: Results of Treatment from 1902 Through 1938 (Preliminary Report). *Proc. Staff Meet. Mayo Clin.*, 15:625, 1940.
62. Walters, W., Lewis, E. B. and Lemon, R. G.: Primary Partial Gastrectomy (Polya Type) for Duodenal Ulcer. *S. G. & O.*, 71:2, 1940.
63. Weiss, E.: Psychosomatic Medicine. J. B. Lippincott Co., Philadelphia, 1944.
64. Winkelstein, A., Cornell, A. and Hollander, F.: The Medical Treatment of Peptic Ulcer Refractory to Sippy Therapy. *Surgery*, 17:696, 1945.
65. Woldman, E. E.: The Treatment of Massive Gastro-Duodenal Hemorrhage by the Continuous Administration of Colloidal Aluminum Hydroxide (A Report of 144 Cases). *Am. J. Dig. Dis.*, 8:39, 1941.
66. Wolf, S. and Wolff, H. G.: Human Gastric Function. An Experimental Study of a Man and His Stomach. Oxford University Press, 1943.
67. Wolf, S. and Wolff, H. G.: The Gastric Mucosa, "Gastritis" and Ulcer. *Am. J. Dig. Dis.*, 10:23, 1943.
68. Discussion of Preceding Papers. *Ann. Surg.*, 121:633, 1945.

Studies of the Effects of High Lipid Diets on Intestinal Elimination. III. Unsaturated Glycerides with Special Reference to Triolein.

By
HELEN L. WIKOFF, Ph.D.,
WARREN R. HOFFMAN, B.A.,
and
JEAN CAUL, Ph.D.*
COLUMBUS, OHIO

THE PRESENT INVESTIGATION is a continuation of some studies of the effects of high fat diets on intestinal elimination. In a previous communication (1), the effects of saturated glycerides fed to dogs were noted. These studies were carried out to determine why a group of human subjects (2) fed diets containing large amounts of fried foods, pastries and other fat-rich articles, reported contradictory results with respect to intestinal elimination. Dogs were used as subjects in our experiments in order to avoid the mistakes in interpretation which human subjects, submitting their own reports, might make.

Since unsaturated fatty acids also occur in the glycerides in foods, the present investigation is concerned with some unsaturated materials. Oleic acid is said to be the most widespread of all natural fatty acids (3). It forms more than half of the total fatty acids in very many fats and is present to the extent of at least ten per cent of the total fatty acids in most fats. So far, it has been found absent from no natural fat or phospho-lipid. Linoleic and palmitoleic acids are other unsaturated fatty acids present in many natural fats, although not nearly so prominent as oleic acid.

Since oleic acid is the most widely distributed of all of the naturally occurring fatty acids, pure triolein was added to the standard diets fed to our dogs. We were unable to obtain sufficient quantities of the pure triglycerides of other unsaturated acids for feeding purposes. However, some preliminary experiments with linseed oil were made and these are included in this report.

PROCEDURE

Three of the dogs* used in our previous experiment were used as subjects. These dogs were kept indoors in separate cages from which they were removed for periods of exercise. Each dog received the contents of a one-pound can of Pard** once a day at a common

feeding time. When added fat was to be included in the diet, the contents of a can of Pard (454 gm.) were thoroughly mixed with the calculated amount of fat in a mortar. The dog was then allowed to eat directly from the mortar. If he did not eat all of his food, it was removed from the cage after half an hour and no more food given until the next regular feeding time, 24 hours later.

As in the previous experiment, information about the intestinal behavior of the dog was gained by direct observation and by chemical examination of the feces, the fecal material being collected as quickly as possible after defecation. Each special diet was fed for three consecutive days. The second day's ration was identified by a marker in order to show the time required for the food to pass through the alimentary canal.

Chemical examination of the feces included moisture, total lipids, lipids soluble in neutral ether and soap fat. Iodine and acid numbers were determined for the lipid fractions, the fractions being isolated and purified as in our previous investigations (1).

DISCUSSION

Olive oil contains nearly eighty per cent triolein and is frequently classed as a mild cathartic in doses of 15 to 30 cc. taken 2 or 3 times daily (5). It was, therefore, not surprising that triolein behaved as a laxative when added to the Pard diet of the dogs. The larger dogs, C and R, ate a diet containing 20 per cent triolein but the smallest dog, W, was made ill by such a diet. Following these feedings the stools of dogs C and R were loose, moist and poorly formed. All three dogs ate a Pard diet containing 10 per cent triolein. Following this diet, the stools were soft and moist but moderately well formed. TABLE I contains the analytical data from the feces of the dogs fed the triolein diets.

Examination of TABLE I reveals several facts. When dogs C and R ate the diet with 20 per cent added triolein, the total percentage of lipids in the feces was less than when the diet with ten per cent triolein was fed, although, as noted above, the laxative effect was greater with the 20 per cent diet. There were more fecal soaps when a ten per cent triolein diet was fed to dogs C and R than when a plain Pard diet was fed. This is the only instance in any of our investigations where the quantity of fecal soaps present on a high fat diet has exceeded or even equalled the amount of fecal soaps

*Dog C, a mixture of hound and collie, weighing about twenty-three pounds, and the fox terriers R and W, weighing seventeen and thirteen pounds, respectively.

**Sufficient canned Pard to complete these studies was provided through the courtesy of the Research Division of Swift and Company.

From the Department of Physiological Chemistry, The Ohio State University, College of Medicine. Aided by a grant from the Comly Research Fund of The Ohio State University.

*Present Address: Arthur D. Little, Inc., Cambridge, Mass.
Submitted August 15, 1945.

on the plain Pard diet. However, dog W did not show any increase in fecal soaps on the ten per cent triolein diet.

The acid numbers of all lipid fractions of the feces of dogs C and R on the twenty per cent triolein are appreciably higher than normal and indicate the probable presence of a free fatty acid. The soap extracts in particular, with values corresponding to molecular weights of 397 and 200 respectively, suggest the possibility of oleic acid (molecular weight 282) in the soap. The iodine numbers of these same fractions are also higher than the normal values indicating the presence

stearic 3.5 per cent, oleic 9.6 per cent, linoleic 42.6 per cent and linolenic 38.1 per cent. This oil was selected for some preliminary experiments because of its relatively high content of linoleic and linolenic glycerides, neither of which were available in pure form.

Linseed oil has been described as a mild cathartic (6) and so it was believed that no particular difficulty would be encountered when a diet of Pard containing ten per cent added linseed oil was fed. Dog C did eat the diet unhesitatingly. However, normal elimination followed and no laxative effect was produced. Dog R was very reluctant to eat the diet and fecal elimination

TABLE I

Analysis of Fecal Material Collected from Dogs Fed Triolein and Linseed Oil in Measured Quantities

Diet	Dog	Per Cent Moisture	Per Cent Lipids				Iodine Numbers			Acid Numbers		
			Total Lipids	Neutral Ether Extract	Soap Extract	Soap Fat By Calculation	Total Lipids	Neutral Ether Extract	Soap Extract	Total Lipids	Neutral Ether Extract	Soap Extract
Pard	C	69.9	20.3	2.9	18.0	17.4	8.0	27.2	5.6	52.8	49.4	59.9
20% Triolein		73.8	15.6	12.5	2.9	3.1	94.9	101.4	95.6	108.2	87.6	141.3
10% Triolein		74.3	32.3	11.0	20.8	21.3	59.5	83.5	36.0	45.2	9.0	42.0
10% Linseed Oil		72.6	16.4*	5.5	10.9	-	-	108.5	27.0	-	4.3	36.2
Pard	R	73.9	19.5	9.3	7.6	10.2	5.1	6.4	25.1	48.6	38.9	54.2
20% Triolein		75.4	21.4	17.8	4.2	3.6	88.8	93.1	39.1	97.6	88.3	280.4
10% Triolein		72.0	38.1	7.6	30.6	30.5	19.9	52.8	33.6	28.0	15.1	40.2
10% Linseed Oil		76.2	30.9*	17.3	13.5	-	-	164.8	51.8	-	5.0	32.4
Pard	W	74.8	17.4	5.0	13.1	12.4	12.9	18.2	12.0	36.2	29.1	43.4
10% Triolein		76.1	10.6	8.2	1.9	2.6	96.8	99.7	108.5	114.4	76.1	111.5
10% Linseed Oil		76.4	7.7*	4.6	3.1	-	-	138.9	32.3	-	14.9	40.8

*By Calculation

of unsaturated material. However, as the iodine number of triolein is only 85 and that of the free oleic acid 89, is it impossible to explain higher values merely as unabsorbed triolein or as free oleic acid or its salts.

The acid numbers of the fecal soaps from dogs C and R on the ten per cent diet of triolein indicate either the presence of acids of much higher molecular weight than oleic acid or the occurrence of appreciable quantities of non-titratable material in the soap fraction. The iodine numbers of the same material show that it is also considerably more saturated than pure oleic acid. On the other hand, the fact that the iodine numbers of the neutral ether extract and of the total lipid fraction are higher than the normal values while the acid numbers are lower than the normal values indicates that some unchanged triolein is probably present in these fractions.

Dog W, somewhat smaller than the other two dogs and unable to tolerate the higher fat diet, behaved similarly to dogs C and R when fed the ten per cent triolein diet. The total lipids did not equal those on a simple Pard diet, but the soap fat was less than normal and the neutral ether extract greater than normal as was the case with the other dogs on the twenty per cent triolein diet.

Linseed oil (4) has been reported to consist of glycerides of the following acids: palmitic 5.4 per cent,

became scanty. Dog W was constipated for 48 hours when fed the diet.

The moisture content of the fecal samples was elevated in every case although no laxative action was noted. (TABLE I) No agreement exists between the per cent of lipids in the various fractions. However, the high iodine numbers and the low acid numbers of the neutral ether fractions indicate the probable presence of unsaturated triglycerides in those fractions. The correspondingly low values for the soap extracts indicate that neither fatty acids nor unsaturated material were present to any extent in the soaps.

Further studies with the pure triglycerides of linoleic and linolenic acids are necessary in order to determine which, if either, of these acids was responsible for the effects noted.

SUMMARY

1. Measured amounts of triolein were added to a diet of standard dog food and fed to dogs to determine the effect of the unsaturated glyceride on intestinal elimination.
2. Triolein added to the normal diet of the dogs acted as a mild cathartic.
3. If the dog could tolerate an addition of twenty per cent triolein to his diet, the percentage of total lipids in the feces was less than when he was fed a diet with only ten per cent added triolein.

4. Measured amounts of linseed oil were also added to the standard diet in order to study its effects on intestinal elimination in dogs. Linseed oil was used because pure glycerides of linoleic and linolenic acids were not available in sufficient quantities to be used for feeding purposes.
5. Linseed oil produced constipation in the smaller dogs and had no effect on the largest animal.

CONCLUSIONS

No general conclusions can be drawn concerning the effects on intestinal elimination produced by feeding diets rich in unsaturated glycerides. Triolein, the triglyceride of the most widely distributed of all naturally occurring fatty acids, produced a laxative effect when added to the standard diet in either ten or twenty per cent concentrations. When the lower concentration of triolein was fed to the larger two dogs, more total lipids

and more soap extract were present in the feces than when the higher concentration was fed. The low acid and iodine numbers of the soap extract after the diet with ten per cent triolein added indicate that the soap extract did not contain appreciable quantities of oleic acid. When the twenty per cent diet was fed to these same dogs, oleic acid was apparently present in the soaps.

If the effects produced by linseed oil were caused by the rather large per cent of linoleic and linolenic acids present in its glycerides, then it might be assumed that the presence of glycerides of one of these acids or of both of them in the diet would cause constipation. Further investigations will be needed to clarify this point. However, it can be said that neither of these acids was present to any extent in the soap extract because the low iodine and acid numbers exclude such a possibility.

REFERENCES

1. Wikoff, Helen L., Caul, Jean F. and Marks, Bernard H.: Some Effects of Diets Rich in the Glycerides of Saturated Fatty Acids on Intestinal Elimination. II. *Am. J. Dig. Dis.*, 10:393, 1943.
2. Smith, Clayton S.: A Comparison of the Digestibility of Meals Prepared with Animal versus Hydrogenated Vegetable Cooking Fats. *Ohio State Med. J.*, 39(5):425, 1943.
3. Hilditch, T. P.: The Chemical Constitution of Natural Fats. P 5, John Wiley and Sons, Publishers, 1940.
4. *Ibid.*, P. 125.
5. Goodman, Louis and Gilman, Alfred: *Pharmacological Basis of Therapeutics*. P. 309. The Macmillan Co., Publishers, 1941.
- Mulines, Michael G.: *Pharmacology*. P. 289. Oxford University Press, 1944.
- Davison, Forrest Ramon: *Synopsis of Materia Medica, Toxicology and Pharmacology*. P. 171. The C. V. Mosby Company, 1944.
6. Goodman, Louis and Gilman, Alfred: *Pharmacological Basis of Therapeutics*. P. 768. The Macmillan Co., Publishers, 1941.

Benign Ulcer of the Caecum

By

C. D. L. CROMAR, MAJOR,

ROYAL CANADIAN ARMY MEDICAL CORPS

MONTREAL, CANADA

CASE REPORT: On the 23rd of June, 1944, a Naval Officer, aged 57 years, was admitted to Rideau Military Hospital. For three days he had suffered from a pain in his abdomen. It had started as a vague, indefinite feeling of discomfort around the navel, but had later developed into a dull ache in the right lower quadrant. This was his only complaint. He was not nauseated and had not vomited. His bladder and bowels functioned regularly. His previous health had always been good.

He was a robust looking man, although a little overweight. His temperature on admission was 99.8° F., his pulse rate 84, and his respirations 20 to the minute. Complete physical examination elicited nothing remarkable except some acute tenderness in the right iliac fossa and rigidity of the lower part of the right rectus abdominis muscle. The tenderness could not be reproduced by digital palpation of the rectum. A leucocyte count showed 19,100 W.B.C.'s per cu. m.m. of blood. Urinalysis showed albumen graded 1.

Immediate coeliotomy was elected in the belief that the patient was suffering from "acute appendicitis" al-

though "perforating neoplasm of the caecum" was considered a possible alternative diagnosis on account of the patient's age. Under spinal anaesthesia a small Lanz incision was made in the abdominal wall. The appendix was readily accessible and was delivered into the wound without difficulty. It was not diseased. The caecum was then palpated gently and in the lateral wall directly opposite the ileo-caecal valve an indurated mass was encountered which measured about 5 cms. in diameter. By enlarging the original incision laterally for about 10 cms. it was possible to visualize this mass and to explore the remainder of the peritoneal cavity. Numerous discrete, firm lymph nodes measuring anything up to 2 cms. in diameter were felt in the substance of the right mesocolon and in the ileo-colic angle. The liver appeared to be free from disease. The obvious diagnosis now appeared to be "adenocarcinoma of the caecum with lymphatic metastasis." Accordingly the terminal ileum and the right half of the colon were resected in one stage along with their mesenteries and continuity of the bowel was re-established by anastomosing the ileum to the middle of the transverse colon.

Aseptic end to end anastomosis was carried out using the Martzleff-Borget technique with a Parker-Kerr basting stitch of 000 catgut for the inner layer and interrupted Halsted sutures of No. 0 black silk for the outer. Five mgms. of sulfanilamide were applied along the suture lines as advocated by Varco. Peritoneum was sutured over the raw area left by removal of the right half of the colon and 10 grammes of sulfanilamide powder were dusted into the general peritoneal cavity. The incision was closed in layers without drainage.

The patient stood the operation well and convalesced smoothly. The cutaneous sutures were removed on the tenth post-operative day, by which time the wound had healed soundly and the patient was free from symptoms.

He remained in hospital for another week, mainly to regain strength and was discharged, recommended for 28 days convalescent leave. He returned from leave in excellent health, suffering no distress and able to eat or drink anything. A barium series taken on August 22nd, 1944, just two months after the operation, showed that there was no obstruction at the site of anastomosis. Barium flowed freely from ileum into colon two and half hours after ingestion.



Fig. 1 — Retouched photograph of the excised specimen. The point of the pencil indicates the crater of the ulcer lying in the lateral wall of the caecum directly opposite the ileo-caecal sphincter.

The resected specimen was examined immediately after the operation. It consisted of terminal ileum, caecum, appendix, ascending colon, hepatic flexure and about half the transverse colon along with portions of the mesentery and the right mesocolon. In the lateral wall of the caecum at the level of the ileo-caecal valve there was a hard spherical whitish mass measuring about 5 cm. in diameter. In the centre of this mass on the mucosal surface was a deep funnel-shaped crater measuring 1 cm. in diameter and penetrating through all coats of the bowel to within the substance of an epiploic appendix on the serosal surface. The base of the ulcer was reddish and was covered with necrotic material. In its gross appearance this ulcer differed in no way from those in the series of sixty-one small cancers of the large bowel which I have reported previously. The firm raised edges of the ulcer and the presence of numerous enlarged hard nodes in the mesentery carried all the hallmarks of malignancy. It was not until sections had been exam-

ined under the microscope that the true nature of the condition could be recognized. Sections from the margin of the ulcer showed no degenerative change in the mucosa but the remaining layers of the wall of the bowel were oedematous and totally disorganized by a widespread exudate of acidophilic fibrinous material and the whole thickness of the bowel was densely infiltrated with large numbers of lymphocytes plasma cells and eosinophiles. The cellular exudate extended to the serosal surface and in some areas the mononuclear cells were collected in large abscess-like foci. Nowhere was there a sign of malignancy. Sections of the lymph nodes showed them to be involved in a similar inflammatory process which was accompanied by extensive extravasation of red blood cells. This then was not a cancer but a benign ulcer of the caecum.

DISCUSSION

Benign ulcer of the colon was first described by Cruveilhier in the year 1830 but it is still an uncommon disease for in the year 1939 Cameron reviewing the literature of over a century was able to find records of only 68 cases. About half of the ulcers have occurred in the caecum and ascending colon and have been situated with greatest frequency in the lateral wall of the colon diametrically opposite the opening of the ileo-caecal valve. According to Barlow the age incidence is highest between 25 and 50 years but cases have been reported in persons aged from 18 to 80 years. Males are affected more commonly than females, especially when the lesion is situated in the right side of the colon. Coincident ulceration of the stomach and duodenum has been reported in 4% of cases. The aetiology of the disease remains obscure. A host of theories have been advanced and have included inflammatory circulatory, neurogenic, bacteriologic, toxic digestive and purely mechanical explanations. Many of these are strongly reminiscent of the oft-repeated but still unproven theories which are supposed to explain the occurrence of ulceration in the stomach and duodenum. An "anaemic spot" has been described in the caecal wall. Lymphoid degeneration, local endoarteritis and even the faint acidity of the chyme which passes through the ileo-caecal sphincter have all been indicated as possible aetiological factors. It used to be thought that inflammatory disease of the caecum occurred most frequently in countries where coarse cereals formed the staple diet of the poorer classes but the late Sir David Wilkie expressed the belief that these diseases had become even more common in Scotland after meat had been largely substituted for the vegetable matter in the diet of the people. Cutler has postulated a relationship between simple ulcer of the caecum and the subsequent development of cicatricial enteritis but this does not appear to be in accordance with the findings of Hadfield in connection with this disease. As stated by Barlow the concrete facts seem to be that the great majority of the ulcers occur at sites of relative stasis and reports stress the funnel-shaped perforating type of ulcer with frequent erosion of muscles. The edge is often hard and relatively chronic but the base may be active suggesting a lesion of slow onset which has suddenly become

acute. Sixty-six per cent of reported ulcers of the right side of the colon had perforated when they were first seen.

The clinical symptoms usually resemble those of appendicitis but cases have been reported where the presenting symptoms have been gastro-intestinal haemorrhage, formation of a mass resembling a neoplasm, stenosis of the gut leading to obstruction, or sudden perforation of the ulcer followed by general peritonitis. Only one case has ever been diagnosed correctly prior to operation. In this case Bombi' made the diagnosis by means of a barium enema.

Treatment must be operative. No case treated conservatively has survived. The surgical measures which have been employed are 1) Simple drainage with 100% mortality. 2) Oversewing the ulcer, with drainage. 3) Local excision of the ulcer, with drainage. 4) Resection with primary anastomosis. 5) Exteriorization resection. The mortality of cases treated surgically has been 40%.

Obviously the treatment to be adopted in any given case must depend upon the condition which is discovered at the time of operation. Primary resection would appear to be the method of choice, where the lesion has not yet perforated. It is the only certain method of

dealing with a disease which cannot with certainty be differentiated from carcinoma until the excised specimen has been subjected to careful histologic scrutiny. Where the lesion has perforated it may be necessary to adopt less radical measures. Simple drainage is not enough but closure of the perforation by suture with drainage or exteriorization of the lesion with drainage together with exhibition of sulfonamides might well suffice.

SUMMARY

1) A case of benign ulcer of the caecum has been reported where the patient was operated upon in the belief that he was suffering from appendicitis and a hemicolectomy was performed because the lesion was thought to be malignant.

2) The available literature has been reviewed.

3) Benign ulcer of the caecum is a rare disease of unknown aetiology which occurs chiefly in the male sex. It has a strong tendency to cause perforation of the bowel. The symptoms are usually mistaken for those of appendicitis. At operation the lesion may resemble carcinoma of the colon. Conservative treatment is invariably fatal. The operative mortality is about 40%. Primary resection with re-establishment of the continuity of the bowel is the procedure of choice.

REFERENCES

1. Bagen, J. A., Cromar, C. D. L. and Dixon, C. F.: Arch. Surg., 43:186-191, 1941.
2. Cruveilhier, J.: Atlas d'Anatomie et Pathologie, Rectum. 4:1830.
3. Cameron, J. R.: Brit. J. Surg., 26:526-531, 1939.
4. Barlow, D.: Brit. J. Surg., 28:575-581, 1941.
5. Wilkie, D. P. D.: Surgery, 1:655-665, 1937.
6. Bombi, G.: Policlinico (Sez. Prot.), 36:1550-1554m, 1929.
7. Harrison, H.: Arch. Surg., 40:959-972, 1940.
8. Rosser, C. Ann. Surg., 119:377-383, 1944.

The Correlation of Intestinal Protozoa and Enteric Microorganisms of Known and Doubtful Pathogenicity.

By
OSCAR FELSENFELD, M.D., M.S.
and
VIOLA MAE YOUNG, M.S.
CHICAGO, ILL.

CONFLICTING OPINIONS concerning the pathogenicity of intestinal protozoa are often recorded in the literature. While *Endamoeba histolytica*, *Giardia lamblia* and *Balantidium coli* are unquestionably considered to be disease producing agents, the position of other organisms belonging to these phyla has not as yet been clarified. Some authors believe that *Endolimax nana*, *Iodamoeba butschlii* or *Dientamoeba fragilis* may provoke diarrhea (1-3). *Chilomastix mesnili* is listed as pathogenic by certain investigators (3, 4). Other workers, however, do not believe that these microorganisms can cause disease (5-7). Similar differences

of opinion occur in the evaluation of the pathogenic power of bacteria present in many fecal specimens, particularly the *Protei*, paracolon bacilli, *Alcaligenes* and *Pseudomonades*. At the present time, however, many investigators are accepting the two most important members of this group, i.e., *Protei* and paracolon bacilli, as potential pathogens, especially in children. The above enumerated bacteria are frequently found in diarrheic stools, concurring with "accepted" pathogens, as *Shigella*, *Salmonella*, *E. histolytica*, etc., and in cases of diarrhea where microbes generally considered as pathogenic could not be revealed with the aid of the usual laboratory tests.

While reports on the investigation of the accom-

panying bacterial flora in bacillary diarrhea are frequently encountered, very little is known about the occurrence of Enterobacteriaceae in protozoan infections. The writers of this article were unable to find comparative statistics showing the frequency of "doubtful" pathogenic bacteria and protozoa in the same series of diarrheic stools. It seemed necessary, therefore, to perform investigation in this direction, in order to clarify the role of both groups of organisms in human disease. An effort was made to receive material suitable for both bacteriologic and parasitologic study. Laboratories using the services of this Enteric Center were asked to furnish permanent hematoxylin stained slides for the study of protozoa and bacteriologic cultures or preserved fecal specimens. During the last three years specimens from 404 cases of amebic dysentery; 13 patients infected simultaneously with *E. histolytica* and either *Salmonella* or *Shigella*; 39 *Salmonella* or *Shigella* infections; 830 diarrheas in which no "generally recognized" pathogen was found and the etiology of the disease was unknown, were studied for

the presence of bacteria and protozoa and the results compared with the findings in 237 persons who did not have diarrhea. The statistics were evaluated with the aid of the routine mathematical methods. The calculations and detailed statistics correlating each species of protozoa and type of intestinal microbe are too lengthy to be incorporated in this article.

Only 23, or 5.1 per cent of the patients with *E. histolytica* and 3, or 5.7 per cent of the cases infected with *Shigella* or *Salmonella*, or with the combination of these latter microbes and *E. histolytica*, did not have *Proteci*, paracolon bacilli or both in their stools. On the other hand, only 11, or 4.6 per cent of the persons not having diarrhea showed *Proteci* or paracolon organisms in their fecal specimens. This evidence indicates that there is doubtless a connection between the appearance of these microbes in the stool and diarrhea. In the case of diarrhea of unknown origin, however, a higher number of persons, 15.6 per cent, did not reveal *Proteci* or paracolon organisms.

TABLE I demonstrates the summary of the findings of intestinal protozoa in all of the examined cases. Statistical evaluation of this table shows the following features:

1. *E. histolytica* was found in a far lower number than was expected in persons not having diarrhea. This may be due to the fact that more than one-half of the healthy controls were medical students recently arrived in Chicago from the relatively lightly infected Eastern states.

2. Other amebas were found in an increased number in all of the diarrheic stools excepting those caused by known bacterial pathogens. There was, however, no significant difference in the increased percentage of these amebas in the varying types of diarrhea. It should also be noted that *D. fragilis* was present in a higher number of stools in the absence of recognized pathogens.

3. Flagellates were found more frequently in diarrheic stools than in fecal specimens from healthy individuals. The average rate of *Ch. mesnili* in diarrheic stools from cases where no known pathogen was found, 9.1 per cent, is somewhat higher than in fecal specimens showing the presence of *E. histolytica*. The same holds true for *G. lamblia*.

4. *Giardia*, *Trichomonas* and small flagellates are more often found in the presence of *Proteci* and paracolon organisms than in the absence of these microorganisms.

The unusual high per cent of small flagellates in these statistics may be explained by a real epidemic of these infestations during the winter 1943-1944 in the Midwestern states.

The simultaneous finding of *Proteci* and paracolon bacilli on one hand, and flagellates of doubtful pathogenicity on the other in the absence of generally accepted pathogens, presents a problem. While our statistics clearly point to the necessity of including *D. fragilis* and *Ch. mesnili* at least among the potential pathogens, the frequent finding of *Trichomonas*, *Embado-*
monas and *Enteromonas* in amebiasis rather gives the

TABLE I
The Occurrence of Intestinal Protozoa

A. Amebas												
Condition	No. of Cases	Absolute Number					Per Cent					D. frag.
		<i>E. hist.</i>	<i>E. coli</i>	<i>E. nana</i>	<i>I. but.</i>	<i>D. frag.</i>	<i>E. hist.</i>	<i>E. coli</i>	<i>E. nana</i>	<i>I. but.</i>	<i>D. frag.</i>	
Amebiasis	404	404	185	201	9	5	100	48.5	49.8	2.2	1.2	
<i>E. histo. a.</i>												
Salm. or Shig.	13	13	4	4	2	0	too small for evaluation					
Salm. or Shig.	39	0	14	17	1	1	too small for evaluation					
No known path. but Pr. or paracolon pres.	718	0	351	319	9	16	0	49.9	44.4	1.2	2.2	
No known path. no Pr. or paracolon found	112	0	45	47	5	5	0	40.2	41.9	2.7	4.4	
No diarrhea	237	10	62	31	4	2	4.2	26.1	13.1	1.7	.8	
B. Flagellates												
Condition	No. of Cases	Absolute Number					Per Cent					Gla. lamb.
		<i>Chil. mesn.</i>	<i>Tricho.</i>	<i>Emb. int.</i>	<i>Ent. hom.</i>	<i>Gia. lamb.</i>	<i>Chil. mesn.</i>	<i>Tricho.</i>	<i>Emb. int.</i>	<i>Ent. hom.</i>	<i>Gia. lamb.</i>	
Amebiasis	404	19	25	38	40	9	4.6	7.9	9.9	9.9	2.2	
<i>E. histo. a.</i>												
Salm. or Shig.	13	1	2	1	0	1	too small for evaluation					
Salm. or Shig.	39	1	3	1	1	1	too small for evaluation					
No known path. but Pr. or paracolon pres.	718	62	63	61	60	57	8.6	8.6	8.4	8.3	7.9	
No known path. no Pr. or paracolon found	112	14	8	7	6	3	12.3	7.2	6.2	5.3	2.7	
No diarrhea	237	4	4	2	2	3	1.7	1.7	.9	.9	1.3	

E. histo. = *E. histolytica*; *I. but.* = *I. butschli*; *D. frag.* = *D. fragilis*; *Chil. mes.* = *Ch. mesnili*; *Tricho* = *Trichomonas*; *Emb. int.* = *Emb. intestinalis*; *Ent. hom.* = *Ent. hominis*; *Gia. lamb.* = *G. lamblia*; *Salm.* = *Salmonella*; *Shig.* = *Shigella*; *Pr.* = *Proteci*; *paracolon* = paracolon organisms; *path.* = pathogen; *pres.* = present.

impression that they only accompany other organisms. Because of recent accumulation of proof in favor of the pathogenicity of many *Proteus* and paracolon strains, the writers do not feel justified in ascribing a pathogenic role to those protozoa which occur with similar frequency in diarrheas of differing origin. It will be necessary to carry out further studies, as to the differentiation of dubious Enterobacteriaceae according to species and varieties, analysis of the gram positive and mycotic flora, quantitative estimation of the protozoa and their relation to the aforementioned organisms, before a final conclusion can be reached concerning organisms causing diarrhea.

SUMMARY

Specimens from 404 patients with amebic dysentery,

39 cases of salmonellosis and bacillary dysentery, 13 mixed infections, 830 persons suffering from diarrhea of unknown origin in which no microbial cause could be found and 237 healthy controls were examined by bacteriologic and parasitologic methods. The mathematical evaluation of the statistics showed that not only *Salmonella*, *Shigella*, *E. histolytica* and *G. lamblia*, but also *D. fragilis* and *Ch. mcsnili* should be included in the list of potential pathogens, while the pathogenic power of *E. nana*, *I. butschlii*, *Trichomonas*, *Embado-monas* and *Enteromonas* was not revealed by the statistics. Because of the growing accumulation of proof for the pathogenicity of several types of *Proteus* and paracolon bacilli, it is imperative to examine diarrhetic stools for all potential pathogens.

REFERENCES

1. Sapero, J. J.: Clinical Studies in Nondysenteric Amebiasis. *Am. J. Trop. Med.*, 19:497-514, 1939.
2. Rothman, M. M. and Epstein, H. J.: Clinical Symptoms Associated with the So-called Nonpathogenic Ameba. *J. A. M. A.*, 116:694-699, 1941.
3. Manson-Bahr, Sir Ph.: Synopsis of Tropical Medicine. The Williams and Wilkins Company, Baltimore, 42-43, 1943.
4. Mackie, T. T., Hunter, G. W., III, and Worth, C. B.: A Manual of Tropical Medicine. W. B. Saunders Company, Philadelphia and London, 209-210, 1945.
5. Craig, C. F. and Faust, E. C.: Clinical Parasitology. Lea and Febiger, Philadelphia, 70-117, 1940.
6. Culbertson, J. T.: Medical Parasitology. Columbia University Press, New York, 83-85 and 112-117, 1942.
7. Belding, D. L.: Textbook of Clinical Parasitology. D. Appleton Century Company, New York and London, 99-142, 1942.

Jejunal Cancer --- A Case Report

By

IMRE BRAUN, M.D.

NEW YORK, N. Y.

PRIMARY MALIGNANT TUMOR of the small intestine is an extremely infrequent lesion. Morrison (1) discovered only 21 primary tumors of the small intestine in his 13,131 autopsies. Among these two were adenocancers. According to the most recent survey by Mayo and Nettrour (2), the incidence of cancer of the small intestine was 0.47% of the total gastro-intestinal cancer. Up to 1931, Kalayjian (3) collected 77 reported cases of carcinoma of the small bowel. This author was able to complete his report with an additional 35 case reports, bringing the total to 112 known cases up to the publication of his article. Nickerson and Williams (4) reported 8 primary cancer of the small intestine in 11,206 autopsies.

The infrequency of this neoplasm is the more remarkable in that the small intestine follows the stomach and precedes the colon, which two organs are together the seat of more than 40% of all malignant growths. This great immunity of the small intestine to new growths might be caused by the fact that the content of the small intestine is fluid and alkaline and that it has no sharp bends.

The age incidence of this tumor is approximately the same as for other cancers. The reported cases indicate a predominance in male patients at a two to one ratio.

Pathology is usually that of an annular adenocarcinoma constricting in type. Metastases are frequently found early in the mesenteric lymph nodes and peritoneum, then in the liver, lungs, long bones and the dura-mater of the spinal cord, in the order named.

The symptoms of the disease depend largely on the speed of development of mechanical intestinal obstruction by the tumor mass. Cramps and epigastric discomfort might be the chief gastro-intestinal symptoms. Usually there is a history of recurrent short episodes of intestinal obstruction associated with cramps, nausea and vomiting. There is extreme variation in the duration of the colicky pain which may last from a few seconds to two hours. The site of pain is usually in the epigastrium. Weakness and easy fatigability together with general malaise might be present but usually secondary to the gastro-intestinal symptoms. Loss of weight occurs in almost every case. The degree of intestinal obstruction appears to be the main factor in the production of vomiting. With a few exceptions, the vomiting is intermittent and follows the other symptoms of the gastro-intestinal obstruction. Constipation, while a common symptom, is too variable to be of diagnostic value. The presence of occult blood in the stool is a valuable sign and the test should be used more frequently than it is. X-ray examination may be of great help in establishing the correct diagnosis, though the use of barium by mouth may consti-

tute a definite hazard by completing an otherwise incomplete obstruction.

The treatment of the small intestinal cancer is surgery — resection with entero-anastomosis the procedure of choice. If the resection is unfeasible, then a palliative procedure — entero-anastomosis with exclusion; or in a desperate case, temporary enterostomy is advised. The prognosis of carcinoma of the jejunum is not favorable. According to Mayo and Nettrour (2) the average length of life for these patients is 17.6 months after operation, and the operative mortality is about 20%. Although these patients live a relatively short time the relief of obstruction and the comfort of the patient justify the surgical procedure.

I should like to add one case to the existing list of reported cases: This case is of considerable interest because of the long history, the exact pre-operative diagnosis and the successful surgical removal of the tumor.

The patient is a 53 year old white female first seen by me on December 29, 1943. She presented the following history —

Menopause for eight years. She had had occasional digestive complaints but without abdominal pain or marked distension. The first indication of her present illness appeared about two years previously. Before

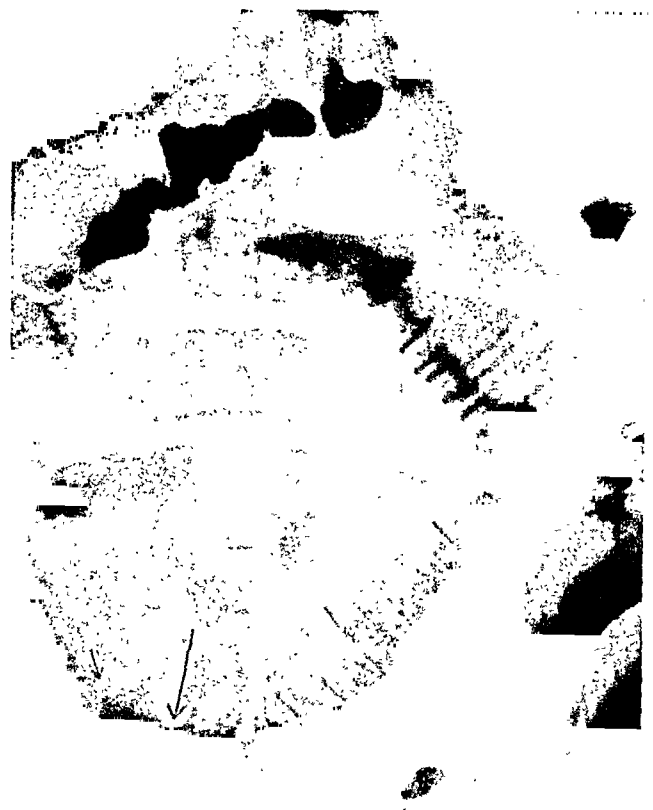
this her appetite was good; she had had no other gastro-intestinal complaints except that of constipation. Two years ago she started to lose weight and up to the time she consulted me she had lost altogether 24 pounds. Her bowel habit had not changed, and her appetite in the last two years seemed to have been diminishing steadily. The stool always appeared normal and was never tarry. Family and past history were essentially negative.

The patient began to complain of indefinite abdominal distress about two years previously. This was unrelated to meals, unaffected by food or alkalies and was accompanied occasionally by nausea and vomiting. The patient was treated variously for indigestion, constipation, menopausal symptoms and nervous stomach. After one year of treatment her condition became worse with periodic attacks of excruciating pain in the abdomen radiating from the umbilicus to the left upper quadrant. At first these attacks were infrequent, lasting only a few seconds and usually were not accompanied by nausea and vomiting. Later they became more frequent, of greater intensity and longer duration. The vomiting occurred more frequently and became more severe. Her last attack occurred five days prior to my consultation. At that time an X-ray study of the G. I. tract had been done and since its completion the



— Braun

Fig. 1 — The appearance of the small intestine two hours after the oral administration of barium. Note the dilatation of the loops of the jejunum.



— Braun

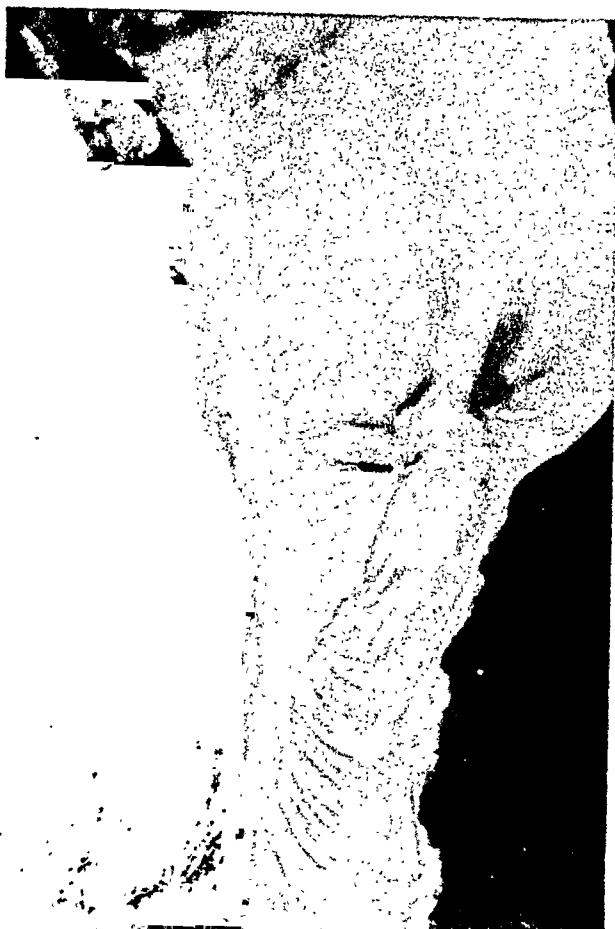
Fig. 2 — Six hours after oral administration of barium. Dilatation of the loops of the jejunum. Note the stop of the barium (arrow).

patient had no bowel movement, the abdomen became distended and the vomiting more persistent. The patient was unable to retain food or fluid.

Examination revealed an acutely ill, dehydrated patient complaining of severe pain in the region of the left upper quadrant. The abdomen was distended and active peristaltic patterns were visible on the left side of the abdomen in the region of the umbilicus. A mass

intestines (Fig. 2). After 24 hour examination some retention was still present in the small intestine (see X-rays).

A diagnosis of an incomplete obstruction due to a neoplasm was made by the X-ray. The clinical picture made it obvious that the incomplete obstruction became complete due to the intake of barium for X-ray study. Immediate operation was decided upon.



— Braun

Fig. 3 — Gross appearance of specimen. Marked annular constriction with dilatation of the proximal loop.



— Braun

Fig. 4 — Same specimen after opening.

the size of a small fist was felt in this area. It was movable, free from the abdominal wall, and in the shape of a sausage — not tender on pressure.

Chest findings were practically negative. Blood pressure was 110/80; the urine showed a trace of albumin — no sugar or acetone were present. The sediment of urine contained a few hyaline casts. The blood count was 4,000,000 red cells, 82% haemoglobin, and 9,000 white cells, 22% band and 65% segment, 8% lymphocytes and 5% monocytes. X-ray study taken five days prior to admission revealed that the stomach was high and hypertonic; the duodenum normal in appearance. After one hour the small intestinal loops were markedly dilated; after two hours a filling defect was found at the small intestine with a proximal distention of the bowel loops (Fig. 1). After six hours only a slight amount of barium was found in the stomach, but most of the meal was retained in the small

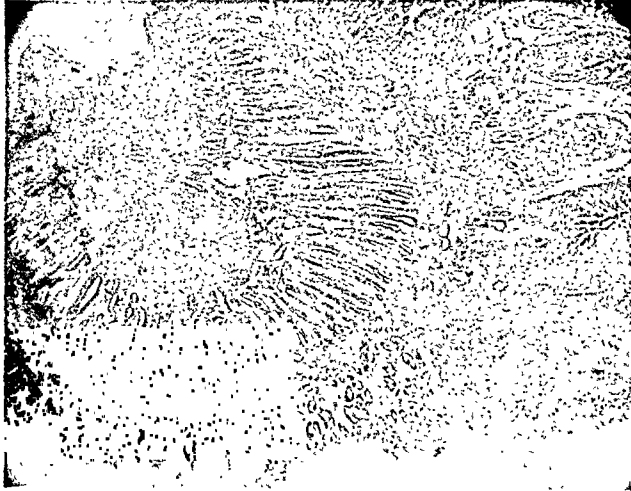
The operation was performed at Sydenham Hospital on December 29, 1943, Case No. 81440. Under spinal anesthesia a long left paramedian incision was made extending from 5 cm. above the umbilicus to 10 cm. below it. Upon opening the peritoneum, no free fluid was found. The upper part of the small intestinal tract was extremely distended and the wall of this part greatly hypertrophied. At the end of this part of the jejunum an obstruction was found in the form of an annular constriction. Below this area, the intestinal tract was normal and partly collapsed. The liver, stomach, and other abdominal organs failed to show the presence of metastasis.

The obstructing lesion was resected with a wedge shape excision of the mesentery (See photograph of specimen — Fig. 3).

After the resection a side to side enteroanastomosis was done and the abdomen closed.

A practically uneventful post-operative course followed this operation during which time the patient received blood plasma twice and for three days Wangenstein apparatus was applied. On the fourth day, the patient was fed by mouth. The patient was discharged 21 days after the operation without any complaint.

The patient has been followed at monthly intervals. She has no complaints and has gained 21 pounds in the past eight months.



— Braunn

Fig. 5 — Microscopic aspect of the tumor with invasion of the intestinal wall.

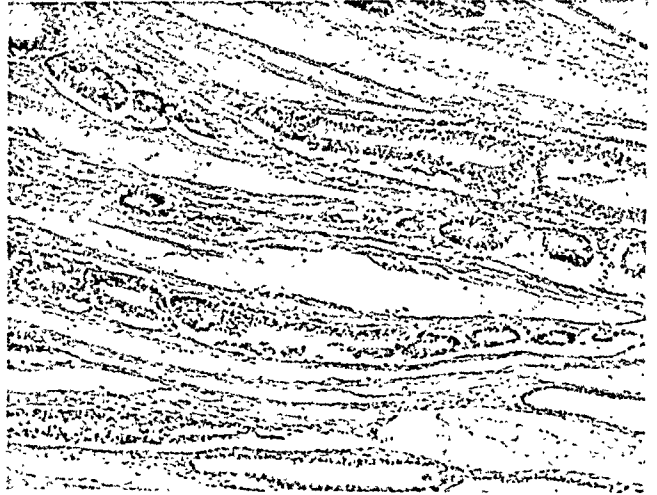
Dissection of the specimen showed an annular constriction of the small intestines. The part of intestine proximal to the constriction was markedly dilated. Below the constriction the intestine was normal. At the site of the obstruction, the wall is thickened to about 1 cm. and very hard (Fig. 3, 4).

The pathological examination of the removed speci-

men revealed that it was adeno-carcinoma of the small intestines infiltrating all coats of the wall (see microscopic photographs — Fig. 5, 6).

SUMMARY

A case of an adenocarcinoma of the jejunum in a female patient of the age of 53 years is described. The clinical and roentgenological findings were those of an incomplete obstruction of the small intestines. The oral administration of the barium suspension for the roent-



— Braunn

Fig. 6 — Highpower microphotograph of the tumor.

genological examination completed the otherwise incomplete obstruction.

The tumor could be removed. In spite of the probable duration of the condition of two years, no metastasis could be found. The post-operative course was uneventful. Re-examination seventeen months after the operation did not reveal any sign of recurrence.

REFERENCES

1. Morrison, J. Edgar: Tumors of the Small Intestine. *Brit. J. Surg.*, 39(113):139, July 1941.
2. Mayo, Charles W. and Nettrour, Walter Scott: Carcinoma of

- Jejunum. *Surg., Gyn. & Obstr.*, 65:303, Sept. 1937.
3. Kalayjian: Cancer of the Jejunum. *Radiol.*, 24:596, Nov. 1937.
4. Nickerson and Williams: *Am. J. Osteop.*, 13:53, 1937.

Medical Management of Pyloric Obstruction Resulting from Peptic Ulcer.

By
SAMSON A. SELEY, M.D.

BROOKLYN, NEW YORK

PYLORIC OBSTRUCTION causing gastric retention for twenty-four to forty-eight hours or more is not an infrequent complication of peptic ulcer. It has been generally considered that such a complication must of necessity be treated surgically. The purpose of this paper is to show that the majority of these cases can be treated successfully by medical management and to indicate a criterion by which one may determine which cases are amenable to medical treatment and which on the other hand should be subjected to a surgical procedure.

The observations forming the basis of this report are the result of a study of seventy-two cases treated over a period of twelve years, the majority of which have been followed for three or more years.

Of the seventy-two cases, sixty were males and twelve females. The average age at the onset of treatment was fifty-one years, the youngest being twenty-eight and the oldest seventy-eight years. The seventy-eight year old patient was first seen by me in 1934 and is still alive and well. X-rays taken every six months for four years showed no evidence of gastric retention after the first gastro-intestinal series which showed forty-eight hour retention. Ten of the seventy-two cases were operated upon and the findings of severe cicatricial stenosis and peri-duodenal adhesions showed plainly why these patients did not respond to medical treatment. Sixty-two of the patients responded very well to medical management.

Symptoms: The history in most cases is that of recurrent epigastric distress for many years. Often the patient has been treated for peptic ulcer, and in fact at the time of examination the patient is already on a Sippy diet or some modification thereof of frequent small feedings with added alkalis or some form of aluminum hydroxide gel. In addition to his usual epigastric distress the patient may complain of increasing pains and vomiting. The vomiting may occur after each meal, or only occasionally. Night pains relieved by vomiting is a prominent symptom. Vomiting, however, is not always present. A few patients vomited coffee ground material and had tarry stools. The duration of the aggravation of the usual ulcer symptoms may be only a few days or may be several months. There is generally a weight loss of ten to twenty pounds in a few weeks. Appetite may be poor or the patient may be afraid to eat because of the subsequent distress. A frequent complaint is increasing constipation. Occasionally a patient is remarkably free of severe symptoms. There may be no weight loss or vomiting, only

a vague epigastric discomfort and other bizarre symptoms pointing to the diagnosis of "gastric neurosis." A routine gastric analysis occasionally uncovers an unsuspected case of pyloric obstruction. In cases of chronic pyloric obstruction of long standing, the patient may complain of diarrhea instead of the constipation expected in the more acute cases. This may be due to a chronic gastro-enteritis produced by the retained food irritating the intestines over a long period of time. One of the cases of chronic pyloric obstruction whose chief complaint was diarrhea had an immediate cessation of his diarrhea following a gastro-enterostomy performed seven months ago, with no recurrence since.

In severe protracted vomiting, dehydration becomes evident. The patient may develop starvation acidosis and run a low grade fever.

Criterion as to Medical or Surgical Treatment

Pyloric obstruction caused by peptic ulcer is either due to cicatricial stenosis and adhesions or due to spasm and edema or a combination of both factors. If cicatricial stenosis is the predominating factor the patient probably will eventually require an operation. If spasm and edema are the more important factors the patient is amenable to medical treatment.

To determine which of these factors predominates, the patient is lavaged each morning before breakfast for a period of ten days, and a record kept of the amount of gastric material evacuated. If at the end of ten days the gastric retention is no longer present or considerably reduced in amount, it is considered that further medical treatment is indicated. Occasionally despite the fact that there is no retention at the end of ten days, the patient eventually may require an operation. On the other hand, if at the end of ten days there is no appreciable diminution in the retention, it is considered that spasm plays only a minor role and that stenosis predominates, and further medical treatment is contra-indicated.

All the patients, including those which required operation, were considerably relieved of their pain, especially the night pain, and the vomiting either stopped completely or was substantially diminished. Those patients in whom spasm was the predominating factor gained as much as ten pounds in the ten days and the average gain after six weeks was fifteen pounds. Those who had macroscopic blood in the gastric contents showed no blood after a few lavages. A few who had seen tarry stools in the previous weeks noted their disappearance.

All but three of the patients were treated in the office. These three patients were so dehydrated that hospitali-

zation was necessary. About one-third of the patients returned to work before the ten days were over. Occasionally a single gastric lavage relieved the patient of his pain and reduced a marked retention to only a few ounces.

Those cases in which the gastric retention was not appreciably reduced and which were sent for operation were none the worse for the delay. On the contrary, the dilatation of the stomach was reduced, the tone of the gastric musculature was better, and the pain and vomiting had subsided. The patient was a better operative risk despite the failure of the medical treatment.

Office Procedure

All patients with gastric complaints are advised to come to the office without eating breakfast. A complete history and physical examination is followed by a routine gastric extraction done with a Levin tube inserted nasally fifteen minutes after drinking three ounces of 7 per cent alcohol. The Levin tube is attached to a simple gastric evacuator and irrigator, called the Gastro-pump (1), which measures the amount of gastric contents withdrawn. An amount more than six ounces withdrawn from a supposedly empty stomach indicates gastric retention, though occasionally in the presence of hypersecretion there may be six or more ounces. If food is present in the material extracted, and the patient has not eaten since the night before, it is definite proof that there is pyloric obstruction. When retention is found, the number of ounces is charted, a sample removed for gastric analysis, and with the Levin tube left in situ the stomach is lavaged with an alkaline solution of sodium bicarbonate, using one teaspoonful to a quart of warm water. The lavage is continued until there is clear alkaline fluid coming out of the stomach. The average time for such an office procedure, using the Gastro-pump (1) is from ten to fifteen minutes.

Having determined that the patient has a gastric retention, a routine gastro-intestinal x-ray series is taken, the stools are examined for occult blood, the Wassermann blood test, blood count, urinalysis and blood chloride determination are done.

If the gastric retention is apparently due to pyloric obstruction caused by peptic ulcer, the ten day test treatment is begun. Each morning before breakfast the patient's stomach is lavaged, first noting the amount of fluid in the patient's stomach. It is not unusual, if the obstruction is due to spasm and edema, to see a gastric retention of thirty ounces or more, reduced to a few ounces within five days. Simultaneously the pain and vomiting subside and the patient begins to gain weight rapidly.

Diet

The patient is given a bland diet and advised to eat six times daily, breakfast, lunch, and dinner, and a glass of milk or malted milk between meals with instructions as follows:

Do not eat anything not on this list.

If there is anything you do not like, do not eat it.

Drink one glass of milk or malted milk at 10 a. m.,

3 p. m., and 10 p. m.

Do not smoke. Choose from the following list:

Milk, buttermilk, sweet cream, malted milk.

Farina, oatmeal, wheatena, cream of wheat.

White bread, toast, rolls and butter.

Soft boiled or poached eggs. Cream cheese.

Mashed, boiled or baked potato. Fresh green peas.

Any combination of milk and eggs, such as custard.

Cocoa or hot chocolate, sponge cake, fruit juices.

Salt and sugar. Vanilla ice cream.

Medication

1) A multi-vitamin capsule, such as Epi-Vita is given after breakfast and dinner.

2) Rx Tr. Belladonna 16.0.

Gelusil qs ad 360.0., two teaspoonfuls six times daily after meals. Gelusil does not appear to constipate the patient like some of the other aluminum hydroxide gels.

Comment: In many of the cases the patient was already on a similar diet and medication without any relief. In one case I forgot to prescribe the medication, and the patient responded to lavage spectacularly without medication.

It appears that in pyloric obstruction due to spasm a vicious cycle is established. The ulcer produces reflex spasm and edema. The spasm causes gastric retention. The retained gastric contents decay and irritate the ulcer, which in turn causes pyloric spasm. Once this cycle is established, antispasmodics, alkalis, aluminum hydroxide gels and bland frequent feedings are usually of no avail. Only by getting rid of the retained irritating gastric contents can the cycle be broken. This is accomplished by repeated lavages. If repeated lavages fail, it becomes necessary to resort to surgery.

At the end of ten days, and frequently before ten days, if the retention has been reduced considerably or has disappeared, and the patient no longer complains of pain, vomiting or discomfort, lavages are continued at longer intervals and finally discontinued entirely. The variety of food permitted is gradually increased until at the end of eight weeks the patient is on a full sensibly balanced diet.

The average course of treatment is eight weeks. Thereafter the patient is instructed to return for check-up, including gastric extraction, every three months.

CASE REPORTS

The following are three typical case reports with accompanying x-ray findings:

Case 1 — P. K., a man seventy-eight years of age, was first seen by me August 16, 1934. He stated that he had been treated for duodenal ulcer for many years, and that his physician had died a year before. Since then he had occasional epigastric distress which was relieved by taking his physician's prescription powders and by following a Sippy diet. Recently he had begun to lose weight, and in the past three weeks the epigastric pain was unrelieved by diet and powders. In the past week he had had several severe vomiting attacks and was very distressed especially at night.

Physical examination showed an old man who had once been a powerful individual. His height was six feet, four inches, and weight one hundred seventy pounds. He had lost forty pounds in weight in the past two months. Aside

from a slight widening of his aorta the examination was negative. Gastric extraction revealed thirty ounces of gastric contents with free acid of fifty degrees and total acid of seventy degrees. Roentgenograms revealed a defective cap with twenty-four hour obstruction.

The patient refused to consider an operation or even hospitalization. Daily lavage was instituted. At the end of five days his pain and vomiting had completely subsided. After ten days there was no gastric retention. The patient gained fifteen pounds in weight and was placed on a full diet. X-rays were taken every six months for the next four years and there was no retention. At the end of six months he regained all the weight he had lost and now at the age of eighty-nine has no gastric complaints.

Case 2 — J. M., forty-five years old, was referred October 19, 1944, by Dr. Martin Markowitz. He gave a history of epigastric distress after meals for six months which became worse in the past two months. In the past two weeks he vomited almost every meal, and lost twenty pounds in weight. Occasionally the vomitus was coffee ground in character and on occasions there were tarry stools. He was on a strict ulcer diet in addition to which amphi-jel was taken. He had received two intravenous injections of glucose in saline. He refused to go to a hospital.

Physical examination showed an apprehensive man, dehydrated and weighing one hundred forty-three pounds. Aside from some tenderness in the region of the duodenum there was nothing remarkable.

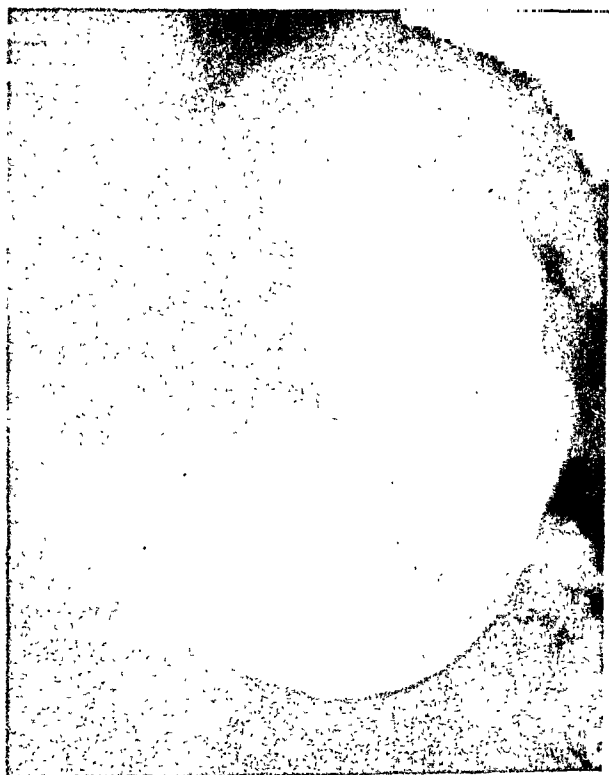


Fig. 1 — Case 1. Before treatment. Dilatation of stomach with defective cap.

Gastric extraction revealed thirty-two ounces of coffee ground material which was positive for occult blood by the benzidine test, with thirty-two degrees of free acid and forty degrees of total acid. Stools were positive for occult blood. Hemoglobin 62 per cent; RBC 3,500,000, Wassermann negative. Roentgenograms revealed pyloric obstruction with forty-eight hour retention. The exact lesion could not be determined.

Due to dehydration I attempted to persuade the patient to be hospitalized, but he was adamant and gastric lavages were begun. October twenty-first, the second lavage showed twenty-one ounces of coffee ground material. Following the second lavage, pain and vomiting ceased abruptly. The third lavage showed ten ounces and the fourth only one and one-half ounces of retained food. The fifth lavage showed no retention at all and the patient "felt fine." His weight had gone down to one hundred and thirty-six, a loss of seven pounds. His appetite was voracious and in a few days he regained the seven pound loss. After the ninth lavage he went back to work and did not return for three weeks. Several more lavages at intervals showed no retention. X-rays taken seven weeks after onset showed no six hour retention. To date pains and vomiting have ceased and the weight went up another ten pounds.

Case 3 — A. F., a male patient, age sixty-three, was seen by me February 5, 1945. History of epigastric distress p. c. for many years. Four months previous he had been operated upon. Ulcer was not found and appendectomy was performed. Epigastric distress was not relieved. In the past two weeks epigastric distress became worse, especially at night, and in the past three days vomiting, induced or spontaneous, gave the only relief. He had developed constipation not present before.

Physical examination revealed an asthenic, dehydrated, anxious elderly male. Weight one hundred and fourteen pounds (a loss of thirteen pounds since his operation four



Fig. 2 — Case 1. Before treatment. 24 hours gastric retention. Defective cap.

months before). Heart and lungs were negative. There was a sense of resistance in the upper right quadrant, but no definite mass or tenderness.

Gastric extraction showed thirty ounces of coffee ground material with prune skins eaten two days before. Free HCl acid forty-eight degrees; total acid sixty degrees. Occult blood reaction to benzidine was markedly positive.

The following morning gastric extraction obtained only nine ounces of gastric contents. The patient had slept through the night before for the first time in weeks.

Roentgenograms revealed a penetrating ulcer on the

posterior wall of the duodenum, with a slight six hour retention, and in twenty-four hours, no retention.

After the sixth daily lavage there was no further evidence of retention, vomiting had ceased, pain almost completely subsided. His weight was one hundred and twenty-one pounds, a gain of seven pounds. After the tenth lavage, his diet was rapidly increased in variety without evidence of retention. On February 21st, sixteen days after onset of treatment, he returned to work.

COMMENT

Case No. 1, the man of seventy-eight, illustrates the value of medical treatment as regards an elderly patient, who may be considered a poor surgical risk. It also illustrates that a cure effected by medical treatment may endure for many years, the patient being now eighty-nine years old. The roentgenograms repeated every six months for four years revealed that there was no gastric retention demonstrable. In addition to the fact that the patient was free of gastric symptoms.

Case No. 2 is of interest, because the man failed to be relieved by a Sippy diet, antispasmodics, aluminum hydroxide gel, and intravenous glucose, but responded rapidly to gastric lavage, despite the fact that due to an oversight the lavages were not supplemented by any medication.

Case No. 3 is one of a few cases in which a single



Fig. 3 — Case 1. Before treatment. 48 hours gastric retention.

lavage alleviated all symptoms immediately, so much so that whereas the gastric extraction revealed food eaten one or two days before, the roentgenograms taken after the lavage showed only slight six hour retention.

Review of Methods of Medical Treatment of Pyloric Obstruction in Recent Literature

The method of treatment outlined in this paper applies largely to ambulatory cases, most of which have

been treated in the office.

In 1941 S. Allen Wilkinson (2) outlined a hospital procedure used at the Lahey Clinic. A Levin tube is inserted through the nose of the patient with obstructive symptoms and the entire gastric contents aspirated. Then through the tube, three ounces of malted milk made with water or three ounces of peptonized milk is introduced every hour on the hour. The tube is clamped for thirty minutes, so that no drainage from the stomach is permitted. At the end of thirty minutes, the tube is unclamped, the tip of the tube is lowered below the level of the patient beside the bed into a bottle and the stomach is allowed to drain by siphonage. Thus, the patient has a fluid mixture of three ounces introduced into his stomach once an hour. The tube is clamped for thirty minutes of each hour and is allowed to drain for thirty minutes of each hour. A record of the total fluid intake through the tube is kept and accurately charted. The total output into the drainage bottle is also accurately charted and these totals are computed for each consecutive twelve hours. It will be seen that this method allows the stomach to function for half the time but also allows the stomach to be emptied and the retained secretion and contents of the stomach to be evacuated for half of the time of each



Fig. 4 — Case 1. Three months after onset of treatment. Stomach normal size. Defect in cap less pronounced.

twenty-four hours. This alternate feeding and drainage is continued throughout the twenty-four hours, day and night, and the total amount of fluid given by tube is approximately seventy-two ounces daily.

In severe obstruction, or in obstruction which is complete, it is obvious that seventy-two ounces or more will be drained through the tube into the drainage bottle. In moderate obstruction, a certain proportion of the fluid contents of the stomach will pass through the pylorus and an amount less than seventy-two ounces will be returned. By comparing the amount returned daily over a period of three or four days, it is easily and quickly determined whether the obstruction is being relieved and whether the emptying of the stomach is returning to normal. In most cases of duodenal ulcer

with obstruction and in particular if the obstruction is due to edema and spasm, the relief of the obstruction is obvious within twenty-four hours and the drainage promptly falls to only four or five ounces for twenty-four hours. Under these circumstances the tube can be withdrawn and, if the diagnosis is still in doubt, the stomach can again be checked by roentgenograms and this time the diagnosis should be fairly obvious. If, on the other hand, the drainage persists in a fairly large amount after three or four days, it has been well established as a clinical fact that it will not be reduced by further drainage, and the case immediately falls into the surgical group.

In addition to this alternate feeding and drainage, it is important to pay special attention to the fluid balance of the patient; he should be given intravenous glucose or glucose and saline solution in fairly large quantities during the period the tube is down. Parenterally, vitamins, especially vitamin B, is indicated, and in the

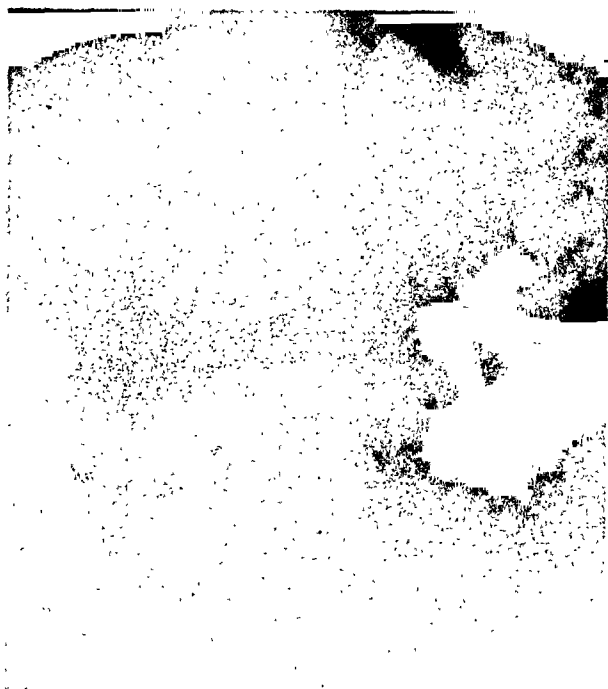


Fig. 5 — Case 1. Six hour film. No gastric retention. Three months after onset of treatment.

presence of high gastric acid values, aluminum hydroxide gel may be helpful.

If after three or four days' observation the return drainage amounts to twenty ounces or more in twenty-four hours, operation is indicated. The stomach at this time will be found to be collapsed, gastric tone improved and the patient will be in much better condition for operation than if he had been operated upon at admission.

In 1941 E. N. Collins and H. R. Rossmiller (4) described the following procedure in the Surgical Clinics of North America. Wangenstein drainage is instituted during the night hours. If the progress of the

patient is not favorable, such drainage is run during part of the daytime hours also. A five day test run is given. The Levin tube is not left in place continuously during the five day period, because it is believed that this may increase the tendency toward post-operative pulmonary complications if surgery is indicated. The amount obtained by aspiration or drainage as related to the amount of fluid taken orally furnishes a means of appraising the course of the disease. Two drachms of aluminum hydroxide gel is given every two hours during the daytime and one ounce at bedtime, midnight, 2 a. m. and 4 a. m. Sodium phenobarbital is given hypodermically at night. Diet consists of six ounces of liquid or semisolid food, such as gruels, malted milk, plain gelatin, junket, ice cream, egg nog given every two hours ending at 6 p. m. Whole milk and cream are avoided because curd formation interferes with both the emptying and lavage of the stomach. Additions to the diet are made as rapidly as tolerated. Parenterally vitamins, antispasmodics such as atropine, and sedatives such as sodium phenobarbital are administered. Liquid petrolatum or cascara is used to prevent constipation.

At the end of the five day period, if the obstruction is relieved, treatment as for uncomplicated ulcer is continued. Persistence of obstruction warrants surgical intervention which usually reveals cicatricial stenosis.

Collins and Rossmiller feel that even if the obstruction has been relieved by medical treatment, operation should be advised if the patient gives a history of previous pyloric obstruction. In their experience, in these instances there is some degree of stenosis, and obstruction is likely to recur if surgical procedures are not used. They conclude, on the other hand, if the patient is seen during his first attack of pyloric obstruction and this is relieved within the five days of medical management, unless there are other indications for operation, continued medical management may prove to be preferable to operation.

In 1937 Henry A. Rafsky (3) described a method of treatment used at the Lenox Hill and Beth Israel Hospitals. His observations were based on a series of twenty-six cases observed over a period of from three to ten years. Six of the twenty-six cases had to be operated upon. Several different methods were used. Eleven cases were treated by duodenal alimentation, a procedure which Rafsky felt enabled him to decide much more quickly whether he was dealing with spasm or stenosis. In certain cases of stenosis the pylorus may be sufficiently patent so that roentgenographically there will be no six hour retention; however, if the duodenal tube with the bead attached fails to enter the duodenum in a few days, it is presumptive evidence that surgery is indicated. A number of roentgenograms were presented showing how edema and spasm subside sufficiently after lavage so that an ulcer not visualized before treatment becomes apparent after treatment.

In 1940 George L. Laporte and George Laporte, Jr. (8), described nine cases of pyloric obstruction with twenty-four hour retention treated with bland diet and alkalis and diathermy every second day over the pylorus

with complete recovery of eight of the nine and partial improvement of the ninth case. Several had not done well on bland diet and alkalis until diathermy was instituted.

SUMMARY

1) A series of seventy-two patients with obstructive peptic ulcers, treated medically, were observed over a period of twelve years.

- 2) Sixty patients (83.3 per cent) apparently recovered without operation.
- 3) An office procedure for the treatment of such cases is outlined.
- 4) Review of methods of medical treatment of pyloric obstruction in recent literature.
- 5) A criterion is suggested to differentiate between stenosis and spasm as the etiologic factor of the obstruction.

REFERENCES

1. Seley, S. A.: The Gastro-pump. *Am. J. Dig. Dis.*, 5:(No. 6), (August) 1938.
2. Wilkinson, S. A.: Medical Management of Pyloric Obstruction. *Surg. Clin. N. Amer.*, 21:735, (June) 1941.
3. Rafsky, H. A.: Non-surgical Treatment of Pyloric Obstruction Resulting from Peptic Ulcer. *N. Y. State J. Med.*, 37:1539, (September) 1937.
4. Collins, E. N. and Rossmiller, H. R.: Obstructive Symptoms Versus Pyloric Obstruction; The Importance of Medical Management. *Surg. Clin. N. Amer.*, 21:1495, (October) 1941.

5. Scriver, Walter de M.: A Case of Pyloric Obstruction Responding to Medical Treatment. *Canad. M. A. J.*, 24:99, (January) 1941.
6. Jordan, Sara M. and Kiefer, E. D.: Complications of Peptic Ulcer, Their Prognostic Significance. *J.A.M.A.*, 103:2004, (December 29) 1934.
7. Kogan, D. A.: Zur Differential Diagnostik Zwischen Pylorus Stenose und Spasm. *Archiv. fur Verdauungskr.*, 55:76-81, (Jan.) 1934.
8. Laporte, George L.: Conservative Treatment of Pyloric Obstruction with Diathermy and other Measures. *Med. Rec.*, 152:133, (August 21) 1940.

Book Reviews

The Venous Pulse and Its Graphic Recording. Franz M. Groedel. 223 pages, 7 illustrations and 290 tracings on 114 Figures (\$5.50). Brooklyn Medical Press, New York.

Groedel's newest book is not only of interest for the cardiologist but also for the gastroenterologist. At about the beginning of this century a limited number of scientists — Franz M. Groedel among them — recognized the importance of phlebography as a means for the study not only of cardiac irregularities, but also for the study of the mechanical events during a heart cycle. Groedel in his monograph shows how these events are mirrored not only in the venous pulse, but also in the pulsatory movements of the air enclosed in the lungs (pneumo-cardiogram) and in the oesophagus (oesophago-cardiogram). At this point his book becomes of interest to the gastroenterologist. We therefore restrict our report to the last chapter concerned with the history, technique and evaluation of the oesophago-cardiogram.

About the history and former technique of oesophago-cardiography the following is reported. The investigation of respiratory pressure changes in the esophagus by J. Rosenthal (1880) and the examination of the swallowing process by Kronecker and Melser (1883) had shown that the esophagogram contains waves which are caused by the movement of the heart. Fredericq, who first studied the esophagogram on dogs and man in 1886, emphasized the identity of these tracings with the auricular pressure curve (1908). A sound with a small rubber balloon was introduced into the esophagus, connected with a sphygmograph and inflated.

Groedel's technique is based upon the previously reported method, but greatly modernized. He used Einhorn's cardia dilator. This tube was introduced into the esophagus up to the cardia of the stomach and its outer end was connected with a microphone, as introduced by Groedel for phlebography. The system was inflated with a few cc. of air, because better records were obtained when the tension in the balloon was smaller. The balloon was then drawn out slowly one or two inches at a time, and in each position an esophago-cardiogram was recorded. By means of the Sanborn Tri-beam Cardiette, it was possible to record synchronously the electrocardiogram, preferably Lead CR^s and the heart sounds as reference tracings, eventually also the phlebogram. The latter can of course be furnished beforehand together with the electrocardiogram and the heart sounds. Thus it was possible to analyze the esophago-cardiogram and to compare it with the phlebogram, the electrocardiogram and the heart sounds. Details of the electric side of the technique are given in the preceding papers.

The interpretation of the esophago-cardiogram has varied very much. Rautenberg's first esophagogram (also reproduced in Janowski's publication) was taken simultaneously with a cardio-phonogram. According to the letterings of Rautenberg's curves, the ventricular systolic wave would start before the first heart sound and the auricular systolic collapse wave soon after the second sound. There is furthermore a great discrepancy between Rautenberg's tracing and the curves obtained in the dog by Fredericq (reproduced for instance by Tigerstedt). Some authors found a negative, others a positive auricular systolic wave. Edens, with improved technique, found a positive auricular wave shortly be-

fore the first heart sound and, according to his nomenclature, a positive bifid ventriculo-systolic wave synchronous with the first heart sound, and a bifid D-wave with a peak during the second sound. Benjamins was the first to furnish simultaneous esophago-cardiogram and electrocardiogram. He proved the coincidence of the auricular wave of the esophagogram with the P-wave of the electrocardiogram. The auricular wave is caused by the action of the auricles, whereas all the other waves are caused by the action of the ventricles.

Groedel's excellent records of esophago-cardiograms taken simultaneously with phlebograms, electrocardiograms and phono-cardiograms show that with modern technique esophago-cardiography is comparatively simple and the tracings when furnished with the esophageal sound in correct position are reliable and scientifically elucidating and important. The esophago-cardiogram obtained with the balloon placed below the level of the left auricle is identical with the phlebogram obtained over the jugular bulb with loaded receiver bell. It reflects most of the mechanical events occurring during systole and diastole of the auricle and during the ventricular systole. The action of the left auricle is represented by a positive auricular wave, produced by, and reflecting the a-wave of the vena cava. The ventriculo-diastole part of the esophago-cardiogram forms a heart diastolic wave. When the end of the tube is placed at or above the level of the auricle the auricular wave is negative, because the receiver balloon records here the movements of the auricular wall. The terminal auricular wave, representing probably the closure of the atrio-ventricular valves; the b-waves, caused by the isometric contraction of the ventricles, and the c-complex, the mirror of the isotonic contraction and the ejection phase of the ventricles, are recorded throughout the esophagus.

The first clinical publication about the esophago-

cardiogram appeared in 1881, the last in 1914. After an interval of thirty years Groedel in his book reopens the discussion about the cardiogenetic pressure changes in the esophagus and gives us a new, easily applicable technique for such investigations, which, according to our conceptions, are of the highest interest for the gastroenterologist.

— Franz J. Lust.

Essentials of Clinical Proctology. By Manuel G. Spiesman. Pp. 238, (\$4.00), New York, Grune & Stratton, Inc., 1946.

This text is a brief outline of proctology as practiced by the author. The material is well organized for medical students, and should be of some value to the general practitioner. As with any outline presentation, however, it is of necessity sketchy in many respects. Diagnostic procedures and treatments are mentioned without detail, and operative procedures are generally indicated or listed rather than detailed.

Certain omissions are noteworthy. There is no mention of tattoo therapy or of tattoo-neurotomy in the treatment of pruritus ani. Ambulatory surgical techniques are not presented. Caudal anesthesia is described as a failure in 25 per cent of all cases. In the reviewer's experience it is almost one hundred per cent effective. The author favors intravenous sodium pentothal as the ideal anesthetic, combined with local procaine infiltration. Oil-soluble anesthetic infiltration techniques are not extensively described.

There is a good presentation of the pecten band and pectenotomy, and the author's views on the management of the external sphincter muscle in fistula surgery are of interest.

Illustrations are schematic, and suitable for the outline type of presentation.

Some Effects of Gum Chewing on Gastric Acidity in Healthy Individuals

By

CLAYTON S. SMITH, M.D.,

HELEN L. WIKOFF, Ph.D.,

and

MARTHA E. SOUTHARD, B.A.

COLUMBUS, OHIO

THE RATHER WIDE-SPREAD use of antacid candies and chewing gums for the treatment of self diagnosed cases of hyperacidity (which actually may or may not exist) prompted us to study the effects of plain gum chewing on gastric acidity.

Twelve healthy persons with no apparent gastric disturbances who had served as subjects for several gastric analyses in a previous investigation (1) were used for this study. The standard test meal of crackers and water which had been used previously was employed in this investigation. After the test meal, each subject chewed 2 grams of a chewing gum (composed of chicle flavored with oil of peppermint) for a period of 5 minutes.

In the present investigation the experiments were repeated with the same subjects on several different days. Total and free acidity determinations were made on specimens withdrawn at 15 minute intervals after the test meal. All of the experiments were performed in the morning and the subjects were not permitted to eat after their dinners on the previous evening. Any residual material in their stomachs at the time of the experiment was removed by a stomach pump before the test meal was eaten.

Gastric data including maximum total and free acidities for each subject and the time at which each occurred are included in Table I. Corresponding average values from the gastric analyses for the same subjects when no gum was chewed are also included in Table I for convenience in making comparisons.

TABLE I
Repeated Gastric Acidity Determinations on Twelve Subjects
After Chewing Gum

Subject and Sex	Maximum Total Acidity		Maximum Free Acidity	
	Degrees	Minutes After Meal	Degrees	Minutes After Meal
P. A. — f	51.4	60	30.0	30
	59.0	75	29.2	30
	54.6	60	30.8	90
	47.8	45	28.0	75
	38.2	60	26.4	60
	74.0	60	46.6	75
Average	55	60	31.9	60
Average for Standard Analyses	60.1	70	34.8	72.3

M. B. — f	71.0	60	42.8	90
	82.2	75	56.6	75
	74.0	60	46.0	60
	57.0	90	43.6	90
Average	71.1	71	47.0	79
Average for Standard Analyses	86.5	69.1	45.2	75
D. G. — f	56.8	60	28.0	60
	70.4	60	34.2	60
	58.0	60	32.0	70
	55.8	75	24.0	75
	51.8	45	33.0	90
	56.0	45	23.0	45
Average	58.1	60	29.0	70
Average for Standard Analyses	66.9	60	35.1	60
W. R. — f	48.0	90	34.0	90
	63.2	75	50.2	75
	52.0	60	34.0	60
	57.4	60	40.0	75
	48.4	90	39.2	90
Average	53.8	75	39.1	75
Average for Standard Analyses	65.4	48	40.2	53
D. S. — f	73.2	45	49.2	45
	59.8	75	42.6	75
	71.2	60	40.8	90
	51.0	45	30.4	45
Average	63.8	56	40.8	64
Average for Standard Analyses	64.9	55	34.6	67.5
M. W. — f	59.5	60	58.8	60
	75.2	60	47.8	60
	75.2	60	44.0	75
Average	70.0	60	50.2	65
Average for Standard Analyses	73.7	60	44.5	60
B. M. — m	52.0	60	40.0	60
	57.0	45	46.4	45
	69.8	45	40.0	45
	65.0	30	47.0	30
Average	61.0	45	43.3	45
Average for Standard Analyses	85.5	70	69.9	70
D. M. — m	29.4	30	23.6	30
	46.0	45	32.0	45
	46.0	60	37.8	90
	36.0	30	27.4	30
	30.0	30	21.0	30
Average	37.5	39	28.2	45
Average for Standard Analyses	44.3	42.5	23.7	52.5
J. M. — m	60.0	75	51.4	60
	65.6	45	44.4	45
	68.0	90	34.2	75

From the Department of Physiological Chemistry, College of Medicine, The Ohio State University, Columbus, Ohio.
Submitted October 4, 1945.

TABLE I (Continued)

Subject and Sex	Maximum Total Acidity		Maximum Free Acidity	
	Degrees	Minutes After Meal	Degrees	Minutes After Meal
Average	64.5	70	43.3	60
Average for Standard Analyses	67.2	73	39.7	73
W. M. — m	57.0	60	40.8	60
	61.6	45	45.8	45
	66.0	60	44.8	60
	47.0	45	36.6	75
	70.6	30	46.8	45
	27.8	60	14.4	60
Average	55.0	50	38.2	58
Average for Standard Analyses	67.3	54	51.2	63
G. S. — m	77.8	60	39.8	45
	62.4	75	46.4	75
	64.4	45	45.6	45
	42.4	60	27.6	60
	40.6	45	27.4	60
	58.0	60	31.0	60
Average	57.6	58	37.5	67
Average for Standard Analyses	85.8	58	63.1	85
H. U. — m	67.0	60	41.2	75
	59.0	45	39.0	90
	53.0	60	34.0	75
Average	59.7	55	38.1	80
Average for Standard Analyses	59.1	51	30.8	75

Inspection of the data in Table I reveals a lowering of the total gastric acidity when the subject chewed gum. The average maximum total acidity was less for eleven of the subjects and increased only .6 degree for the remaining subject (H. U.). Although the production of acid was depressed by the chewing of gum, the average time required for the subject to reach the maximum total acidity was not uniformly affected by gum chewing. Five subjects required less time, four needed more time and three persons took just the same time to reach their maximum total acidity as when no gum was chewed.

No characteristic effect of gum chewing on free acidity can be noted in Table I, for the average maximum free acidity increased for half of the subjects and decreased for the other half. The average time necessary for the subjects to reach this maximum free acidity was distributed in about the same proportion.

In order to show more clearly the effect of gum chewing on gastric acidity, average values for the total acidity and for the free acidity at the 15 minute intervals were calculated for each of the 12 subjects. The values compose Table II.

After a subject had reached his maximum acidity, no further data from that particular analysis were included in calculating the average values. It was assumed the stomach was in the process of emptying itself when the gastric acidity began to decline.

The data in Table II show that the effects of gum chewing on gastric acidity were the most pronounced

during the first half hour. The total acidity was lowered in ten of the twelve subjects at the fifteen and thirty minute intervals while the free acidity was depressed

TABLE II

Gastric Acidity at Various Time Intervals under Standard Conditions For Gastric Analyses and After Gum Chewing

Subject and Sex	Time Interval	Average Total Acidity in Degrees		Average Free Acidity in Degrees	
		Standard Analyses	After Gum Chewing	Standard Analyses	After Gum Chewing
P. A. — f	15 min.	21.4	18.6	15.3	12.3
	30 min.	43.5	33.4	26.7	18.9
	45 min.	44.5	43.4	23.1	14.3
	60 min.	53.7	53.3	27.6	26.9
M. B. — f	15 min.	20.8	23.0	10.3	6.9
	30 min.	50.7	39.5	8.5	8.2
	45 min.	66.6	62.6	24.4	20.3
	60 min.	75.6	66.0	35.3	41.3
D. G. — f	15 min.	22.0	15.3	.7	1.4
	30 min.	40.5	36.7	13.5	13.1
	45 min.	54.2	52.0	22.3	15.6
	60 min.	72.3	57.1	28.3	26.5
W. R. — f	15 min.	30.9	12.4	11.2	2.5
	30 min.	48.8	21.3	17.6	10.3
	45 min.	63.8	40.4	28.4	18.7
	60 min.	65.2	45.7	41.0	42.1
D. S. — f	15 min.	20.8	15.4	4.8	6.4
	30 min.	31.5	36.8	4.5	10.1
	45 min.	58.4	56.7	21.2	30.3
	60 min.	66.9	60.7	21.1	28.3
M. W. — f	15 min.	37.2	15.8	8.1	9.1
	30 min.	61.9	42.3	17.1	15.5
	45 min.	70.6	61.9	31.6	28.9
	60 min.	66.7	70.0	37.3	47.2
B. M. — m	15 min.	36.3	26.9	11.3	3.7
	30 min.	57.5	41.4	34.1	29.9
	45 min.	76.5	52.5	52.3	39.1
	60 min.	58.5	60.9	55.9	40.0
D. M. — m	15 min.	11.6	20.2	4.1	12.4
	30 min.	38.3	35.6	15.7	24.0
	45 min.	43.9	44.2	21.8	32.0
	60 min.	41.0	46.0	19.4	36.0
J. M. — m	15 min.	16.6	10.2	6.7	2.2
	30 min.	33.3	31.3	10.8	12.6
	45 min.	55.4	54.2	23.5	33.2
	60 min.	65.4	53.2	29.7	42.7
W. M. — m	15 min.	27.9	17.1	11.0	4.9
	30 min.	44.5	36.4	24.3	16.0
	45 min.	59.9	47.6	33.4	34.1
	60 min.	64.5	50.5	43.0	27.5
G. S. — m	15 min.	37.4	23.7	4.3	5.7
	30 min.	69.1	46.3	28.9	18.0
	45 min.	77.3	52.4	38.1	21.1
	60 min.	89.1	57.8	48.9	31.9
H. U. — m	15 min.	20.4	16.5	11.3	5.6
	30 min.	48.3	49.4	12.7	9.0
	45 min.	56.5	51.0	21.2	22.3
	60 min.	54.0	60.0	26.8	30.8

in nine of the twelve subjects during the same time intervals. After half an hour, the free acid did not seem to be influenced by gum chewing. However, the effects on total acidity could still be noted at the end of an hour since the total acidity was depressed in two-thirds of the subjects at that time.

SUMMARY

The effect of gum chewing on gastric acidity has been studied in the case of 12 individuals from whom normal gastric curves had previously been determined. The chewing of gum depressed the gastric acidity of two-thirds of the individuals during the period of an

hour. Both the total and the free acidity were depressed in five-sixths of the individuals for the first half hour. The maximum total acidity was less in eleven of the twelve subjects when gum was chewed. However, the time required to reach this maximum did not vary materially from the time required when no gum was chewed.

REFERENCES

1. Smith, Clayton S., Wikoff, Helen L. and Southard, Martha E.: Gastric Acidity in Apparently Healthy Subjects. *Am. J. Dig.*

Dis., 12:117, 1945.

Tyrothricin in Proctology

By

ALFRED J. CANTOR, M.D.

FLUSHING, NEW YORK

INTRODUCTION

THE PRACTICAL therapeutic application of antibiotic activity is of relatively recent origin. Investigations of antibiotic activity, however, date back at least to the time of Pasteur. Pasteur noted that "anthrax in susceptible animals can be repressed by the presence of other micro-organisms," an observation made in 1887. Early investigators have also recorded the fact that some soil bacteria produced substances which either inhibited the growth of or destroyed other bacteria. No practical development of the antibiotic agents resulted, however, until the later refinements of cultural techniques and biochemical processes.

In 1922 Alexander Fleming reported the discovery of an antibacterial substance produced by a mold, a species of penicillium, and he named this substance "penicillin." This mold had floated from the air into a culture of *Staphylococcus aureus*, destroying the bacteria. In 1939 René Dubos announced the discovery of an active antibiotic principle precipitated from autolysed cultures of an aerobic spore-bearing soil bacillus (2). This bacillus was identified as the *B. brevis*.

This powerful antibacterial substance produced by the soil bacillus was found to produce lysis of gram-positive cocci, and protected mice inoculated with 10,000 to 100,000 lethal doses of pneumococci, when injected intraperitoneally (3).

Preparation of the bacterial extract (or bactericidal agent) and further purification resulted in the discovery of two crystalline fractions, gramicidin and tyrocidine (5, 11, 12). Tyrocidine was found to be the same as substances previously described as gramidinic acid and graminic acid. "Tyrothricin" is the name applied to the bactericidal substance containing both gramicidin and tyrocidine.

It is important to note that both gramicidin and tyrocidine are potently antibacterial against gram-positive organisms. Gramicidin, however, is 25 to 50 times more

effective than tyrocidine. Gramicidin is ineffective against gram-negative organisms, but tyrocidine, under certain conditions, will demonstrate antibacterial activity against this group.

It is of interest to compare the degree of activity of penicillin and gramicidin in tissue culture (8). Both agents are found to be equally potent against the gram-positive organisms. It is of further significance to note that the combined action of the two substances in the same culture medium does not result in any greater antibiotic activity than when these agents act separately.

Tyrothricin cannot be employed parenterally due to its hemolytic activity (4, 6, 7, 13, 14, 16, 17). The cytotoxic activity of gramicidin (greater than that of tyrocidine) need occasion no concern in its local clinical use. The amount employed clinically will produce no demonstrable tissue damage.

In review we note that tyrothricin is the alcohol-soluble, water-insoluble antibiotic agent containing both gramicidin and tyrocidine, and is derived from autolysed cultures of the aerobic, spore-bearing soil organism the *Bacillus brevis*. Gramicidin is more active than tyrocidine against the gram-positive bacteria, but tyrocidine is active against gram-negative organisms, the meningococcus and the gonococcus. Tyrothricin contains 10 to 20 per cent of gramicidin, and from 40 to 60 per cent of tyrocidine. It is employed only topically or in cavities that have no direct blood stream communication.

CLINICAL PROCTOLOGICAL APPLICATION

The employment of tyrothricin by the author over the past several years has demonstrated its value in proctologic surgery. This antibiotic is now a routine part of the post-operative care in all rectal and open pilonidal surgery.

As an adjunct in the post-operative care of routine hemorrhoidectomy surgery, prolapse, anal ulcer excision, cryptectomy, or the surgery for other relatively non-infected types of pathology, continuous wet dress-

ings of tyrothricin are ordered. These dressings are instituted immediately after the surgery, whether the surgery be ambulatory or non-ambulatory. They are continued by the patient until healing has been completed.

The solution is prescribed as the 20 cc. tyrothricin concentrate (25 mg. of tyrothricin per cc.), to be diluted to 1000 cc. with pyrogen free sterile distilled water. The resulting solution contains 500 micrograms of tyrothricin per cc. When the solution is prepared it is important to add the tyrothricin concentrate to the water. Precipitation occurs upon prolonged standing of this solution, and it should therefore be used as rapidly as possible. If distilled water is not used for the dilution the tyrothricin will precipitate due to the salt or mineral contaminants in the water.

Wet dressings of the tyrothricin solution are applied continuously, and instituted immediately following surgery. Infection is prevented in the "clean" case, such as post-hemorrhoidectomy or anal ulcer excision, and the healing time is reduced. The wounds do not suppurate, drainage is minimal and healthy granulations appear early.

Infections and abscesses of this region are subjected to the usual surgery, and wet dressings of tyrothricin are employed immediately. Suppuration ceases rapidly and healthy healing is soon noted. These wounds become rapidly clean and free from all infection. This is of particular value in the ambulatory patient where drainage may be annoying or incapacitating. These patients may be completely and comfortably ambulatory within twenty-four hours after surgery. They are instructed to carry a small quantity of the tyrothricin solution in a bottle to their office or place of business, and to renew their dressings as often as may be required. The dressings are applied as wet gauze squares, and are held in place by a sanitary napkin (such as Kotex) and an elastic belt. This provides a comfortable, easily applied dressing, and assists in obtaining early ambulation (1).

The use of this solution in the post-fistulectomy patient, especially after extensive and complex fistula surgery, and in the patient who requires wide saucerization of a wound, has markedly reduced the healing time. In the open pilonidal operations, an odorless, relatively drainage-free, and rapidly granulating wound is noted within a short time after the inception of these dressings.

In some cases an annoying, sometimes pruritic perianal dermatitis seems to result from these continuous wet dressings. This dermatitis disappears rapidly after the discontinuance of dressings. When it is deemed essential to continue the dressings despite the dermatitis, the normal skin area bordering the areas of excision are covered with an antipruritic ointment such as Cinna-caine ointment to protect these skin areas.

It should be noted, however, that tyrothricin has been employed in the treatment of eczematoid dermatitis and infectious dermatoses (9, 10, 15), with favorable results. The use of this solution suggests itself in certain types of pernicious pruritis ani. Clinical experience in this direction would be of interest.

Study of tyrothricin by rectal or sigmoidal instillation in the various forms of proctitis and sigmoiditis may disclose interesting findings. Other antibiotic agents will undoubtedly be developed within the next few years, and may provide the answers to some of our presently insoluble therapeutic problems.

CONCLUSIONS

The history and physical properties of tyrothricin are described. Tyrothricin is the water-insoluble, alcohol-soluble antibiotic agent derived from autolysed cultures of the aerobic, sporulating soil organism, the *Bacillus brevis*. It is chiefly active against the gram-positive bacteria.

Applied topically, in a dilution of 500 micrograms per cc. in sterile pyrogen-free distilled water, it is of great value in proctologic surgery. Healing time is shortened, suppuration is reduced to a minimum, and early ambulation is encouraged.

REFERENCES

1. Cantor, A. J.: Ambulatory Proctology. Paul B. Hoeber, Inc., New York, 1946.
2. Dubos, R. J.: Bactericidal Effect of an Extract of a Soil Bacillus on Gram-Positive Cocci. *Proc. Soc. Exp. Biol. & Med.*, 40:311, (February) 1939.
3. Dubos, R. J.: Studies on a Bactericidal Agent Extracted from a Soil Bacillus. II. Protective Effect of the Bactericidal Agent Against Experimental Pneumococcus Infections in Mice. *J. Exper. Med.*, 70:11, (July) 1939.
4. Dubos, R. J.: The Effect of Specific Agents Extracted from Soil Micro-organisms upon Experimental Bacterial Infections. *Ann. Int. Med.*, 13:2025, (May) 1940.
5. Dubos, R. J. and Cattaneo, C.: Studies on a Bactericidal Agent Extracted from a Soil Bacillus. III. Preparation and Activity of a Protein-Free Fraction. *J. Exper. Med.*, 70:249, (September) 1939.
6. Dubos, R. J. and Hotchkiss, R. D.: The Production of Bactericidal Substances by Aerobic Sporulating Bacilli. *J. Exper. Med.*, 73:629, (May) 1941.
7. Heilman, D. and Herrell, W. E.: Hemolytic Effect of Gramicidin. *Proc. Soc. Exp. Biol. & Med.*, 46:182, (January) 1941.
8. Heilman, D. H. and Herrell, W. E.: Comparative Anti-bacterial Activity of Penicillin and Gramicidin: Tissue Culture Studies. *Proc. Staff Meet. Mayo Clin.*, 17:321, (May) 1942.
9. Herrell, W. E. and Heilman, D.: Experimental and Clinical Studies on Gramicidin. *J. Clin. Invest.*, 20:583, (September) 1941.
10. Herrell, W. E. and Heilman, D. H.: Further Experimental and Clinical Studies on Gramicidin. Abstract for Central Society for Clinical Research. *J. A. M. A.*, 118:401, (April 18) 1942.
11. Hotchkiss, R. D. and Dubos, R. J.: Chemical Properties of Bactericidal Substances Isolated from Cultures of a Soil Bacillus. *J. Biol. Chem.*, 132:793, (February) 1940.
12. Hotchkiss, R. D. and Dubos, R. J.: Bacterial Fractions from an Aerobic Sporulating Bacillus. *J. Biol. Chem.*, 136:803, (December) 1940.
13. MacLeod, C. M., Mirick, G. S. and Curnew, E. C.: Toxicity for Dogs of a Bactericidal Substance Derived from a Soil Bacillus. *Proc. Soc. Exp. Biol. & Med.*, 43:461, (March) 1940.
14. Mann, F. C., Heilman, D. and Herrell, W. E.: Effect of Serums on Hemolysis by Gramicidin and Tyrocidine. *Proc. Soc. Exp. Biol. & Med.*, 52:31, (January) 1943.
15. Rammelkamp, C. H.: Use of Tyrothricin in the Treatment of Infections. *War Med.*, 2:830, (September) 1942.
16. Rammelkamp, C. H. and Weinstein, L.: Hemolytic Effect of Tyrothricin. *Proc. Soc. Exp. Biol. & Med.*, 48:211, (Oct.) 1941.
17. Robinson, H. J. and Molitor, H.: Some toxicological and pharmacological Properties of Gramicidin, Tyrocidine and Tyrothricin. *J. Pharmacol. & Exp. Therap.*, 74:75, (January) 1942.

Radiation Therapy of the Cancer of the Esophagus

By

J. BORAK, M.D.

NEW YORK, N. Y.*

THE CANCER of the esophagus is generally considered radio-resistant. This view is not easily explained radio-biologically because over 95% of the esophagus cancers are squamous cell cancers and squamous cell cancers of any other localization are well amenable to radiation therapy with X-rays or radium. Thus we see that the squamous cell cancers of the skin, lips, oral cavity, pharynx, larynx and cervix uteri can be cured with rays when the tumor has not spread beyond the reach of the rays and a definite amount of rays has been applied. The opinion considering the esophagus cancer radio-resistant is also not in line with the fact that, as first shown by Lacassagne, in experiments on animals, the squamous cell epithelium lining the walls of the esophagus reacts to the rays in the same way as the squamous cell epithelium of other organs carrying this type of epithelium.

This reaction has been first described by Regaud in the skin and then by Coutard in the mucosal membranes, and has become the basis of their method of X-ray therapy now generally accepted. The squamous cell epithelium degenerates under the influence of rays and eventually is destroyed electively so that while the surface epithelium undergoes the process of destruction (epitheliolysis), the underlying tissues such as the blood vessels and the connective tissue merely exhibit signs of an inflammation. Both processes, the destruction of the surface epithelium and the inflammation of the submucosal tissues are temporary in nature. The epithelium is regenerated from the not irradiated or less intensely irradiated neighboring areas and the inflammation gradually subsides in the underlying tissues so that within a few weeks clinically a restitution ad integrum results. Watching by means of an esophagoscope the changes which the esophageal mucosal epithelium undergoes during the treatment, as is done during the treatment of larynx cancers by means of a laryngoscope, we see that the epitheliolytic reaction occurs in the esophagus approximately after a similar dose and length of time as in the pharynx and posterior part of the tongue. Thus a dose of about 4000 r (depth dose) given within 4 weeks produces an epitheliolysis which is followed by a clinically complete regeneration after a period of 2 to 3 months.

The possibility of producing an epitheliolysis electively that is of a destruction limited to the surface epithelium is known to be a characteristic of the squamous cell epithelium and foreign to the cylindric and glandular epithelium, a characteristic which presumably accounts for the fact that cancers deriving from a squamous cell epithelium appear to be radiologically curable in contrast to those originating from a cylindrical or glandular epithelium. This is presumably so because a new growth, as long as it proliferates without infiltrating the neighboring tissues, is never less radio sensitive than its mother tissue. Accordingly, if a dose is given producing an epitheliolysis of the nor-

mal epithelium, the same effect is to be expected in the neoplasm deriving from this epithelium. Since an epitheliolysis can be obtained in the esophageal mucosa as in any other mucosal membrane lined with a squamous epithelium, the destruction of esophageal cancers by means of rays appears biologically quite possible.

The similarity of the type of its mother tissue and of its response to rays suggests that the esophageal cancer might not be inherently radio-resistant and that other reasons may account for the difference between the results of radiation therapy in the field of the cancers of the esophagus and that of other squamous cell cancers.

In fact, we see that the esophagus is the only hollow organ in the body that is lined with a squamous cell epithelium. This is so because it has no specific digestive functions but is in the first place a tube for the transit of food from the oral cavity to the stomach. In accordance with this main function are two gross anatomical characteristics of the esophagus, namely its comparatively thin walls and comparatively narrow lumen. These characteristics turned out to be serious handicaps in the radium treatment of the esophagus cancer. The *thin walls* have as a consequence that there is, in contradistinction f. e. to the thickwalled uterus, an inherent danger of a fatal perforation, especially in view of the fact that the radium applicators cannot be placed at any noteworthy distance from the walls but lie closely to them so that a highly intense effect is produced on the adjacent tissues. The *narrow lumen* has a consequence that the tumors readily produce a stenosis often amounting to a complete obliteration so that the radium applicators frequently either cannot be introduced into the narrowed lumen or cannot be pushed through the entire length of the stenotic part.

To sum up we see that the intracavitary radium therapy so successful in the treatment of various malignant lesions for anatomical reasons cannot display its full effectiveness in the field of the esophagus cancer, except in very early stages.

As a result, in the radiological treatment of the esophagus cancers we have to depend on the external radiotherapy alone, or at least, in the main. Here, too, however, there is a difficulty due to the topographical position of the esophagus. There is no other organ lined with a squamous cell epithelium so deeply seated inside the body. The distance between the esophagus and the walls of the chest is 7-8 cm. in its middle part and 10-12 cm. in its lower part, which is most frequently affected. By comparison, the distance in question is 3-4 cm. in the oral cavity or larynx and 6-7 cm. in the naso-pharynx. Now, then, if a dose of 4000 roentgen-units (r) is to be given to an esophagus cancer as is

*City Hospital of New York.

done in other squamous cell cancers, the total dose to be given to the skin with the commonly used X-ray equipment is at least 10,000 r, often 12,000 r and sometimes even more, as compared to 6000-8000 r required in cancers of the larynx or pharynx. The application of such a large amount of rays often taxes the greatest resourcefulness of the radiologist as well as the greatest endurance of the patient. It is from the radiological point of view difficult to distribute the rays in a manner assuring that the high dose required by the disease is concentrated in the tumor without unduly severe reactions to other tissues. And it is difficult for the patient to endure the therapy since the huge dose given to the body must be delivered within a period of time not too long as to diminish the accumulative effectiveness of the rays.

Thus it seems to appear that the unfavorable results in the field of radiation therapy of the esophagus cancers eventuate rather from difficulties resulting from certain anatomical and topographical circumstances than from an inherent radio resistance of these tumors. This is corroborated by the fact that in cases in which the circumstances are less unfavorable so that an adequate dose can be given, esophageal cancers can be made to regress to an extent making all tumor symptoms disappear completely. This applies first of all to the difficulty in swallowing. The patient who prior to the treatment was fed through a gastric fistula because not even fluids could pass the esophagus, can after the treatment drink and eat again in the normal way. Further evidence that the tumor has retrogressed derives from fluoroscopic examination, showing the passage restored in the region in which it was blocked previously. The roentgenograms are particularly impressive because they show that the filling defects disappear and are replaced by normal contours.

The disappearance of the tumor can be ascertained also by means of esophagoscopy. In a few cases even on autopsy no trace of the previous neoplasm has been found (Holfelder, Cathie, Cade, Smithers). The disappearance of esophageal tumors for a period of from 3-10 years was reported by Guisez, Baum, Palugay, Schinz and Zuppinger, Pohle, Levitt, Roberts, Strandquest, Nielsen and others.

Rare as such cases have been, nevertheless, they are remarkable because such results have not been obtained in the cancers of any other part of the digestive tract from the cardia to the rectum, presumably because they derive from a cylindrical epithelium which is known to be inherently less radio sensitive than the squamous cell epithelium. The recognition that the cancers of the esophagus are not inherently radio resistant should stimulate our efforts to improve the results of our treatment by adapting the technique of irradiation to the particular difficulties confronting us in this field. Our radio-therapeutic efforts should the more be stimulated since, despite surgical advances, the majority of the esophageal cancers still does not appear to be amenable to radical surgery.

From what has been said it appears that the radiological treatment of the esophageal cancers should be guided

by the idea that a depth dose of about 4000 r is to be given to the tumor within 4 weeks. For this purpose 2 sessions 6-8 hours apart are performed daily on 5 days a week. In each session 2 fields are treated. Each field is 5 cm. wide and 12 cm. long. The wall nearer to the tumor has three fields, parallel to each other, the opposite wall has 1-3 fields depending on the depth of the tumor. The rays traverse the medial fields, corresponding to the tumor, perpendicularly while treating the adjacent lateral fields the tube is angulated depending on the site of the tumor. The total dose given through the medial fields is larger than that given through any of the lateral fields because they are nearer to the tumor than the latter so that a larger depth dose results. Accordingly, the medial field of the back being the nearest to the tumor, receives the largest dose. The single dose given to the skin in each session depends on the penetrating power of the machines used. With the common 200 Kilovolt machine and with the technical factors applied in the treatment of other deep seated lesions the single dose is 150 skin-roentgens. The total dose varies in accordance with the site of the tumor and the diameter of the chest between 10,000 and 14,000 r as mentioned before. The dose is smaller with the supravoltage X-ray therapy (Buschke and Cantril) and larger with the external radium therapy. The ratio between the skin and depth dose is the only factor that counts.

Large amounts of Vitamin B are given intramuscularly or intravenously to combat the nausea and other symptoms of the ray sickness. At the end of the treatments an intense skin reaction develops. It has the nature of a so called "moist epidermitis" (epidermiolysis) in the medial fields while in the lateral fields a so called "dry epidermitis" (desquamation) develops. The skin reaction does not require any specific treatment. Covered with an Aquafor ointment (Kaplan) it usually clears up within a few weeks leaving no other marks than an intensely pigmented skin.

The results obtained in 2 patients treated according to the principles described above in which the diagnosis of a squamous cell cancer was established microscopically are reported subsequently.

The first patient was 55 years old and suffered for about four months from an increasing difficulty of swallowing. No gastrostomy. The X-ray film showed a considerable narrowing of the lumen of the lower part of the esophagus with ragged, irregular contours. The filling defect was about 5 cm. long. There was also a marked prestenotic dilatation (Fig. 1). The next film shows the condition four weeks later on the day the last treatment was given (Fig. 2). It shows a definite improvement of all radiological signs of the lesion. The contours are smoother and more regular, the filling defect is much less distinct, the prestenotic dilatation is less pronounced. The third film (Fig. 3) illustrates the condition of the patient 17 months after the completion of the treatment. It shows a complete restitution ad integrum with no residual sign of the neoplasm.

The second case concerns a 61 year old man, who was suffering from difficulty of swallowing for seven months. Gastrostomy 2 months before. The X-ray film shows a complete stop of the barium meal at the cardia, at the level of the diaphragm (Fig. 4). There was a very rapid improvement of the symptoms in this case. The film taken four weeks after the start of the treatment shows that the passage and the contours were to a large extent restored. The next film taken six

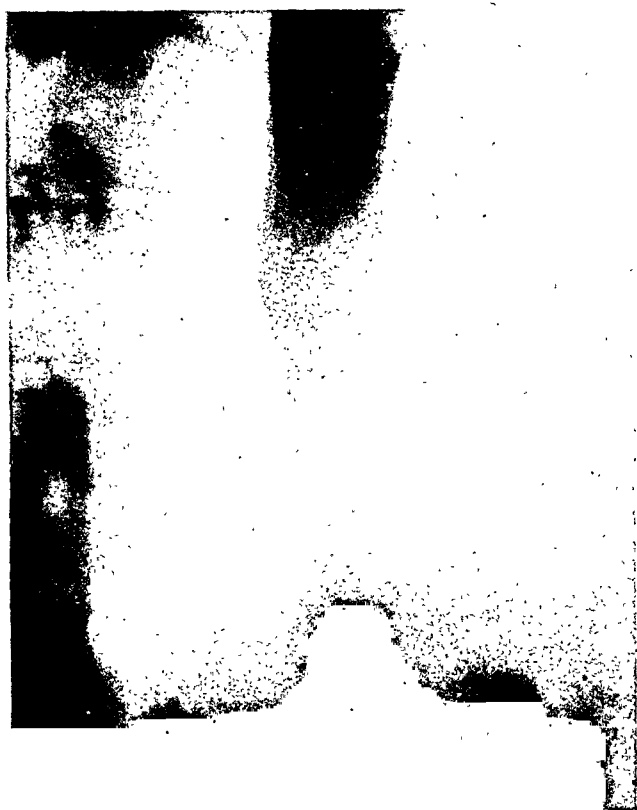


Fig. 1 — The esophagus shows a marked filling defect in its lower part with a considerable narrowing of the lumen.

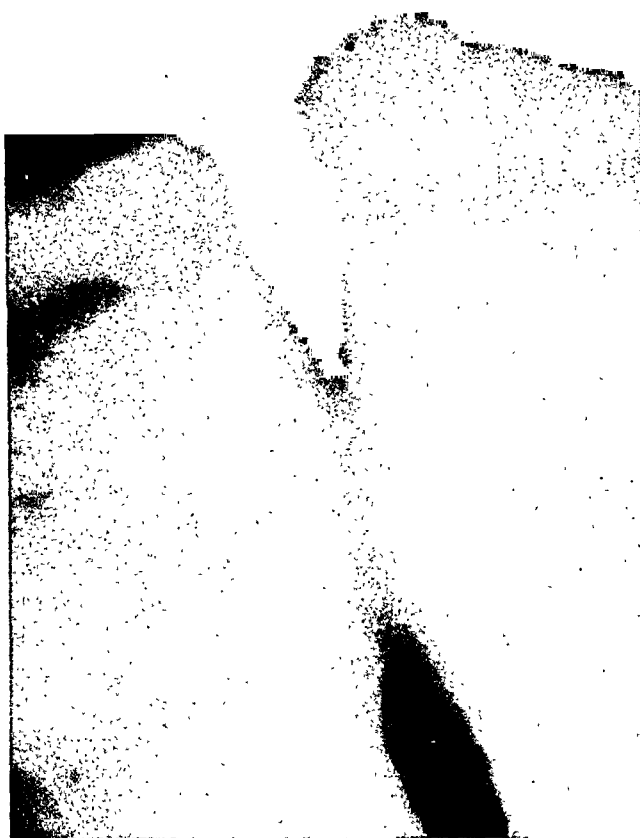


Fig. 3 — Same case as in Fig. 1, 17 months after the completion of X-ray therapy.



Fig. 2 — Same case as in Fig. 1, 4 weeks later, on the day of the last X-ray treatment.



Fig. 4 — The esophagus shows an unpassable stenosis at the level of the cardia.

weeks later shows that the improvement made further progress so that almost a normal appearance resulted (Fig. 5). This result has lasted so far for 21 months.

Thus, in the two cases in which the cancers received a dose of about 4000 r in four weeks a disappearance of the clinical symptoms as well as the radiological signs of an esophageal neoplasm resulted and there is so far a symptom free survival amounting to 17 months in one case and to 21 months in the other. Needless to emphasize that we cannot speak of a cure because a local recurrence as well as distant metastases may develop.

Needless also to stress that parallel results are not to be expected in all cases with an esophagus cancer. When metastases in the mediastinal lymphnodes are present, when the tumor invaded the muscles and deeper layers of the esophageal walls, when the tumor is too extensive, the result cannot be satisfactory. One thing, however, appears to be certain, namely, that the esophagus cancer is not radio-resistant. It is true that certain anatomical and topographical characteristics of the esophagus render the radiological treatment of the esophageal cancers technically very difficult, sometimes to an extent making it quite impractical. However, in cases in which the circumstances are more favorable, the cancer of the esophagus appears to be amenable to radiation therapy as any other squamous cell cancer.

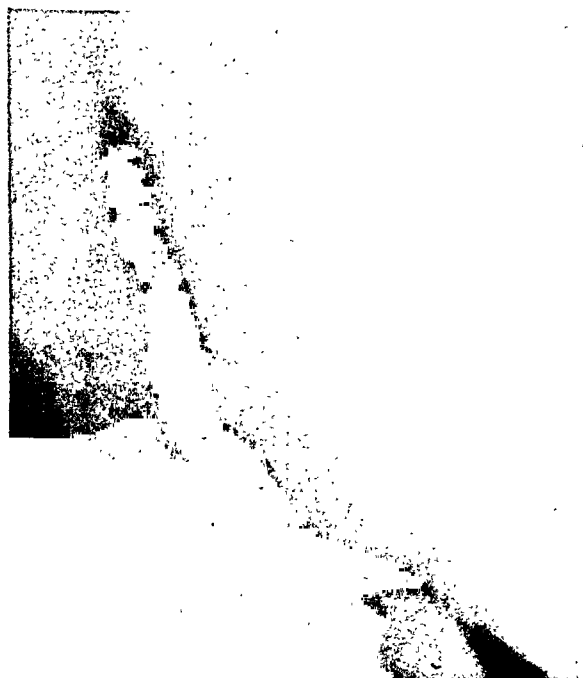


Fig. 5 — Same case as in Fig. 4, 6 weeks after the completion of X-ray therapy. The result has lasted for 21 months.

REFERENCES

Baum: *Radiology*, 27:58, 1936.
 Buschke and Cantril: *Radiology*, 42:480, 1944.
 Cade: *Malignant Disease and Its Treatment with Radium*, 1940.
 Cathie: *Radiology*, 32, 1939.
 Coutard: *Amer. J. Roentgenol.*, 28: 1932.
 Guisez: *Presse Medical*, 1135: 1935.
 Holfelder: in Pohle's: *Clinical Roentgentherapy*, 1938.
 Lacassagne: *Arch. de l'Inst. du Radium*, 141: 1930.

Levitt: *Brit. Med. J.*, 1:1199, 1937.
 Nielsen: *Acta Radiologica*, 21:352, 1940 and 26:152, 1945.
 Palugay: *Strahlen Therapie*, 41:746, 1931.
 Pohle: *Mississippi Valley Med. J.*, 64:45, 1942.
 Regaud: *Acta Radiolog.*, 11: 1932.
 Roberts: *Br. J. Radiol.*, 9:732, 1936.
 Schinz and Zuppinger: *17 Jahre Strahlentherapie des Krebses*, 1937.
 Stranquest: *Acta Radiologica*, 22: 1941.
 Zuppinger: *Ergebn. mediz. Strahlenforschung* 7, 1936.

Continuous Drip Treatment for Chronic Ulcerative Colitis: Preliminary Report

By

JUAN NASIO, M.D.*
 ROSARIO, ARGENTINA

THE RESISTANCE of ulcerative colitis to therapy has been described recently by Bergen (1); and Centeno (2) states, "The treatment of ulcerative colitis, still the subject of study and investigation, at present consists, in the majority of cases, of improvement in the general condition of the patient and in hygienic and dietetic regimen." Udaondo (1929) has pointed out the uselessness of many of the methods suggested because of the complexity of the disease and the variety of etiological factors. Vaccines and serums have

been of uncertain benefit for the specific forms; and complementary treatment, as the use of oxygen or ozone by rectum, and pneumoperitoneum (3), likewise has been unsatisfactory. The usual antiseptic astringent or antispasmodic enemas and insufflation of the colon by catheter or proctoscope have proved irritating and ineffective, and are considered dangerous by Bergen, Buie (4) and other investigators (5). Anticeptic washes through a cecostomy or appendicostomy have been tried but found of little advantage. Since the newer understanding of colonic lesions emphasizes the value of placing the diseased bowel completely at rest, ileostomy, which temporarily isolates the colon, is at present performed with relative frequency. Satisfactory results,

*Chief of Gastroenterology, Rosario Hospital, and Fellow of the National Cultural Commission, Rosario, Argentina. The author is indebted to Wyeth, Incorporated, of Philadelphia, for technical assistance.

Submitted October 6, 1945.

however, are obtained, according to the most favorable statistics (1), in but a small percentage of cases.

Despite advanced knowledge of the anatomical and anatomopathological development of the disease, local symptomatic treatment has never been carried out in a rational manner. While it is true that many chemical substances possessing healing properties are available, the methods of administration heretofore employed have rendered them ineffective. Overemphasis on the concept that ulcerative colitis is not a local but a general disease, and failure to apply an agent with persistent astringent action directly to the lesions have prevented the adoption of conservative therapy; and the physician is obliged either to treat the patient expectantly until spontaneous remission occurs or to resort to surgery.

In ulcerative colitis the glands secreting mucus may be seriously altered. Normal colonic contractions are diminished or cease, with failure of trituration of the alimentary contents; hyperkinesia later may develop. From loss of the absorptive function assimilation of water, salts and other minerals does not occur. Putrefaction and abnormal fermentation enhance the injury to the ulcerated and denuded mucosa; and deformation, stricture and other serious complications eventually may follow.

Local treatment for ulcerative colitis to be effective, therefore, should 1) relieve pain and other symptoms; 2) protect the existing lesions from chemical, bacterial and alimentary trauma; 3) arrest extension of the process and promote healing; 4) correct hyperkinesia; 5) prevent reinfection and complications; 6) restore the normal functions of the bowel.

That the colonic mucosa may be protected and healed by local treatment, either through the rectum or by intubation through the upper digestive tract, now appears feasible. Studies on rectal application of healing substances are in progress and will be described later. The present report concerns the author's experience in the treatment of patients by a continuous drip through intranasal tube (as employed for peptic ulcer), using a colloidal preparation similar in mechanical properties to the normal secretion of the intestinal mucosa. The medication is believed, for physiologic reasons, to have greater protective action in the colon than in the stomach or duodenum; and it is important that it reach the bowel readily and continuously and extend over the entire mucosal surface.

TECHNIC

1) A latex tube, attached to a continuous drip apparatus, is introduced through the nose as far as the cardia. There may be slight discomfort in the nasal fossa the first day, but after forty-eight hours the patient will have adapted himself to the presence of the tube. 2) A 1:2 or 1:3 suspension of kaolin in alumina gel with mineral oil, 500 Gm., to which has been added bismuth subgallate, 50 Gm., is placed in the drip apparatus. Seven hundred grams of the mixture usually is administered in twenty-four hours, although more may be given with safety. 3) Sulfaguanidine or succinylsulfathiazole and any antispasmodic remedy, as 10 per cent paregoric, also may be added if desired.

4) The drip is permitted to flow at the rate of 10 drops per minute the first day, and later increased to 20 drops per minute, as tolerated by the patient. 5) The drip is discontinued for half an hour before and after breakfast and the midafternoon feeding, and for one hour before and two hours after lunch and dinner. During these intervals the patient may be permitted out of bed. 6) Treatment is continued for periods of fifteen days, with rest intervals of no less than a month, and is repeated as necessary.

Six patients with serious ulcerative colitis of six months' to five years' duration have been treated by this method (Table I). Autogenous vaccines had been

TABLE I

Six Cases of Chronic Ulcerative Colitis Treated by Continuous Drip Administration of Kaolin in Alumina Gel with Mineral Oil

Case Number	Age, years	Sex	Married or Single	Duration of Symptoms before Drip Treatment	Stage of Disease at Time of Drip Treatment	Results
1	27	M	S	2½ years	Third	Improvement for 1½ years
2	35	F	M	3 years	Third	Improvement for 1½ years
3	23	M	S	4½ years	Third	Improvement for 9 months; then symptoms recurred, requiring additional drip treatment
4	43	M	M	5 years	Third	Improvement for 4 months; then symptoms recurred, requiring additional drip treatment
5	25	F	S	6 months	Third	Improvement for 1 year
6	29	F	S	8 months	Second	Improvement for 5 months

used persistently in cases 2 and 3 without benefit (Fig. 1). Pneumoperitoneum had been done on patient 4, with no improvement; and sulfasuccidine, administered to the fifth patient, also was ineffective. In all cases at least two series of treatments by the continuous drip method were necessary; and in cases 3 and 4 the symptoms recurred after periods of remission, necessitating further administration of the kaolin-alumina gel mixture. During drip therapy standard dietetic and physiotherapeutic management was carried out in all cases, but no specific treatment was attempted.

RESULTS

In eighteen to forty-eight hours, in all cases, the bowel movements were markedly fewer and of more solid consistency; intestinal pain was diminished, and the discharge of blood and pus lessened. All patients soon manifested general physical progress, with recovery of appetite and weight, and radiologic and proctosigmoidoscopic evidence of improvement, varying with the type and severity of the disease and the length of the treatment period. The roentgenograms showed disappearance of the zones of pseudopolyposis and return of haustral markings (Fig. 2). On visual



Fig. 1 — (Case 2.) Grave idiopathic ulcerative colitis. Roentgenogram after duration of symptoms for three years, with complete failure of former treatment, including autogenous vaccines. Sigmoidoscopy showed granular, moth-eaten, bleeding mucosa corresponding to the third stage of Buie's classification.



Fig. 2 — (Case 2.) Roentgenogram after period of four months, in which patient received three series of continuous drip treatments with dietetic and other supportive measures. Note reappearance of haustral markings, indicating anatomical and functional recovery. During eighteen months following treatment the patient has had one or two painless bowel movements a day.

examination after four months of treatment the recto-sigmoid surface presented scattered small superficial ulcerations surrounded by congested but clean mucosa. Fewer military abscesses were seen.

Because of the large doses of the kaolin-alumina gel mixture administered, the neutralization of gastric acidity in these patients was studied. In 40 per cent the acidimetric curve showed decrease in free acid by comparison with the figures obtained before treatment. The acid-base equilibrium was not disturbed.

COMMENT

The treatment appears to be harmless, with exercise of moderate care, as the preparation is not absorbed but tends to extend over the mucosal surface and to adhere to the alimentary residue moving through the intestinal lumen, with little danger of obstruction.

That the improvement exhibited resulted from the local therapy is suggested by these considerations: 1) the patients received no other medication; 2) in direct roentgenogram of the colon after slight air insufflation the bowel appeared filled by an opaque substance, evidence that the kaolin-alumina gel mixture was in contact with all parts of the mucosal surface (Fig. 3); 3)



Fig. 3 — Roentgenogram of colon after slight air insufflation. The cecum and ascending colon are well visualized; the descending colon is less clearly traced.

symptoms were relieved in eighteen to forty-eight hours after institution of treatment, with fewer and more solid stools, and progressive clinical improvement; 4) early discontinuance of treatment was soon followed by recurrence of symptoms.

This conservative method of treating ulcerative colitis is believed preferable to ileostomy, since the drip treat-

ment isolates only the diseased mucous membrane of the colon, relieves symptoms, promotes healing of the lesions and favors restoration of normal bowel function. However, these findings cannot be regarded as conclusive in view of the limited number of patients studied, the cyclic nature of the disease, and the necessity for a longer follow-up period in which to evaluate results. It is therefore suggested to specialists and physicians in general practice that this method be given further trial.

CONCLUSIONS

1. As the etiology of the various forms of ulcerative colitis is not yet clear, neither effective specific treat-

ment nor a satisfactory method for complementary local therapy heretofore has been available.

2. It is suggested that the continuous drip administration of a colloidal adsorptive and astringent substance (a mixture of kaolin in alumina gel with mineral oil and bismuth subgallate) be used.

3. Six cases of serious chronic ulcerative colitis are described, in which symptomatic relief occurred in eighteen to forty-eight hours after drip treatment was begun, with progressive clinical, roentgenographic and rectosigmoidoscopic evidence of improvement.

4. In two cases symptoms recurred after remission for several months, necessitating further drip treatment.

5. The treatment appears harmless and attended by little danger of intestinal obstruction.

REFERENCES

1. Bagen, J. A.: The Present Status of Ulcerative Colitis and Regional Enteritis. *Bull. N. Y. Acad. Med.*, 20:34, 1944.
2. Centeno, A. M.: Colitis Ulcerosa Crónica. *Anal. Disp. Nac. Enf. Ap. Digestiva*, 5:537, 1942.
3. Neuman, H.: Treatment of Chronic Ulcerative Colitis by Pneumoperitoneum. *Brit. Med. J.*, 1:9, 1943, London (Abstracted in *J. A. M. A.*, 121:1416, 1943).
4. Buie, L. A.: *Proctología Práctica*. Salvat. Edit., Barcelona-Buenos Aires, 1943, p. 507.
5. Streicher, M. H.: Chronic Ulcerative Colitis. *J. A. M. A.*, 118:431, 1942.
6. Fradkin, W. Z.: The Control of Rectal Bleeding in the Convalescent Ulcerative Colitis Patient. *J. Lab. & Clin. Med.*, 22:896, 1937.
7. Eyerly, J. B. and Breuhaus, H. C.: Treatment of Ulcerative Colitis with Aluminum Hydroxide and Kaolin. *J. A. M. A.*, 109:191, 1937.

Brief Psychotherapy in the Treatment of Gastro-Intestinal Disorders

By

MALCOLM L. HAYWARD, M.D.*

PHILADELPHIA, PA.

AT THE PRESENT TIME much work is being carried out on the emotional background of gastro-intestinal disorders, especially peptic ulcer and ulcerative colitis. Successful management of these conditions may require prolonged and skilled psychiatric treatment. It is important to remember, however, that often a great deal can be done for patients by means of brief and simple psychotherapy. Time and again I have been surprised by the relief brought to people with apparently profound emotional disturbances when a proper psychiatric approach is employed.

Etiology of Emotional Problems

The primary factor in the development of a lesion of the digestive tract or for symptoms suggestive of such a disease may be a warping of the patient's fundamental reactions to life's problems. Many less complicated situations, however, give rise to emotional unrest which may be expressed as symptoms referable to the abdominal organs. Problems to be looked for include economic reverses, death of a person upon whom the patient was dependent, infidelity of a loved one, and upheavals of the patient's accustomed way of life. In

some manner or other, the patient is out of step with life. His desires have become blocked and he is unable to find a way out of the trap. The resulting tension may be expressed in many forms. Some patients will speak frankly of worry, nervousness, fear or insomnia while in others the tension is expressed as visceral symptoms such as palpitation, feelings of pressure in the chest and epigastrium, or some form of abdominal distress.

Technique of Management

The patients seem to fall into several classes. Those of one group will lose all their symptoms when they are assured that careful objective studies show nothing abnormal. In others, however, no organic pathology can be demonstrated but their symptoms persist. It is then necessary to take extra time for a complete review and elucidation of the case. Alvarez has pointed out that many patients can be cured merely by taking enough history. In these cases the patient has not thought much about his symptoms before coming to the doctor and if a thorough history is taken he may see by himself the connection between emotional tensions and the development of his symptoms. In all cases a very thorough questioning as to the chief complaint should be made. This may seem strange but often it is found that when pressed, a patient who had complained of abdominal discomfort will admit that what really bothers

*Instructor in Medicine, University of Pennsylvania School of Medicine.

From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic, Hospital of the University of Pennsylvania.

Submitted October 12, 1945.

him most is a terrible nervousness or restlessness. If the somatic symptoms are still held as the only complaint, the doctor should ask directly, "Do you think that nervousness and unhappiness have anything to do with your trouble?" Patients who deny any emotional problem are difficult to treat. They should be told kindly but firmly that all their studies are negative, that their symptoms are due to some hidden emotional disturbance, that medical treatment can do nothing more for them and that they should consult a psychiatrist. This is particularly true of patients who demand an operation. It is far better to lay one's cards on the table and lose a patient than to allow a useless operation and subsequently be blamed for symptoms supposedly arising from adhesions or the like.

Attitude of the Therapist

When a patient admits that nervous tension is a large factor in his problem one should begin a thorough investigation of the causes for this. At the start of treatment, sedation and a bland diet will do much to decrease the severity of the symptoms and will increase the confidence of the patient in the doctor so that psychotherapy is more readily accepted. The attitude of the doctor is all important for success. He should show patience, kindness and a genuine desire to help. The patient with an emotional problem can be roughly compared to a man trying to hold an inflated balloon under water. In both cases, constant effort is required which in the patient is expressed as nervousness, tension, restlessness, worry or irritability. If this concept is kept in mind it becomes clear that the doctor should try to discover and get rid of the cause of the tension. One can never make progress by scolding or arguing with the patient. Instead one must constantly ask leading questions. Good examples are, "When did this trouble first appear? What changes came into your life at that time? What things upset you most? At what time of day do you feel worst? What are you doing at that time? What are you really worrying about? What do you want that you can't get? What would make you happy?"

This process of questioning must be carried on slowly and patiently. The important problems are those that cause the patient most pain and of which he is often most ashamed, so one cannot expect him to discuss them immediately. As soon as the patient is able to look upon the doctor as a friend who is interested in solving his problem, who will never criticize or make fun of him, then he will be glad to discuss his deepest and most painful secrets. He must be led to do this; he cannot be bullied into it.

Gradually the patient comes to speak less of his somatic symptoms and more and more of his emotional problem. Once this is clearly in view he must be helped to find a solution. The important word here is "find," for the doctor must not tell the patient what to do or even give him "good advice." Avenues of outlet from the trap should be discussed but the patient must make the final decision for himself. An emotional problem can be solved only when the patient's desires are satis-

fied and what may seem good to the doctor may be quite wrong for the patient. In all cases the patient should be encouraged to express himself freely, for the release of pent-up emotions can produce so much relief that he is able to decide the next steps in adjustment to the problem without guidance. Do not attempt to reach a decision in a hurry; the patient will be able to decide for himself when he is ready. A great deal of time is not necessary for any one interview but the patient should be encouraged to return as often as desired.

Case 1. B. N., a 59 year old white woman, was admitted to the clinic complaining of dull epigastric pain and pressure. The pain had at first been relieved by food and soda but gradually became almost constant. She had lost considerable weight. Physical examination showed only a marked impairment of vision, while roentgen and laboratory examinations were negative except for an achlorhydria to histamine.

She was placed on a bland diet with dilute hydrochloric acid and phenobarbital medication. This decreased the severity of her symptoms somewhat, but she then began to complain of great nervousness and restlessness. Further study of her case showed that for several years she had been under treatment for a tuberculous uveitis which had nearly destroyed her sight. She was now unable to work and was in terrible fear of the future. The problem was discussed at length and the possibility of attending a school for the blind was suggested. After several interviews she admitted freely that her abdominal symptoms were mostly due to fear and nervousness and stated that coming to the clinic gave her courage. When last seen she was eating well, gaining weight and feeling reasonably comfortable.

Discussion: In a case like this, in which the problem centers about a real handicap, no complete solution of the difficulties may be possible. A great deal was accomplished in reducing this woman's distress, however, so that she was again able to eat well and to maintain her physical condition.

Case 2. F. B., a 60 year old colored woman, was admitted to the clinic complaining of weakness, loss of appetite, weight loss and constipation. The referring physician reported a mass in the right lower quadrant and had made a diagnosis of malignancy. Positive observations were a blood pressure of 160/105 and a large bowel that was palpable throughout most of its length. Roentgen and laboratory studies showed no abnormalities.

A careful review of the case showed that she was chiefly troubled by restlessness and nervousness. She was single and all her life had been active in church affairs and Sunday school teaching. Her complaints had all come on a month prior to admission to the clinic at which time she experienced a sudden attack of weakness and dizziness. She was seen by her physician who told her that she had a high blood pressure and must stop all her work. She followed these directions closely and spent the next three weeks alone at home. During that time she worried continuously about her health and gradually developed her abdominal complaints.

Treatment in this case consisted of bowel training and sedation accompanied by a full discussion of the onset of her illness. She was encouraged to eat anything desired and gradually increase her activities. During the course of treatment she gained 8 pounds and her blood pressure fell steadily, reaching a level of 125/80 at one point. When last seen she was feeling well and required no medication.

Discussion: This case shows clearly how a physician may unwittingly produce a neurosis. It also demonstrates the necessity of a thorough history and a careful evaluation of the chief complaint.

Case 3. W. H., a 68 year old white man, entered the clinic complaining of burning epigastric pain relieved by food but recurring after about two hours. The symptom had been present for about a month and had become increasingly severe with less and less relief from food. His past history showed several episodes of peptic ulcer, which had always responded promptly to an ulcer diet, but in this instance, though he had adhered strictly to a diet with interval feedings and amphojel, there had been no improvement. Physical examination suggested that he was rundown and chronically ill. Over the heart a mitral systolic murmur was heard and auricular fibrillation was present. Localized tenderness was demonstrable below the xyphoid. Laboratory examinations showed no abnormalities except for occult blood in the feces. Radiological study showed a large crater in the stomach, which was felt to be an ulcer, benign or malignant. Gastroscoy was attempted but was unsuccessful due to technical difficulties. Because of the size and the refractory nature of the lesion operation was advised, but he refused this.

He was continued on the strict ulcer regimen, but after two months he was having more pain than ever. He also showed increasing tension and complained greatly of nervousness and insomnia. Consequently an attempt was made to find an emotional background in his condition. The patient was employed as a janitor in a hospital laboratory and was a hard-working, conscientious man. The laboratory had recently come under a new management and because of the war had less help. He was feeling overworked and during the interview was able to express a great deal of resentment toward the management. He stated that he had always tried to do his best and now was being put upon.

Treatment in this case consisted in encouragement to express his resentment followed by efforts to ameliorate the situation. Arrangements were made to lessen the amount of work required of him and it was explained to the patient that it was not from malice but because of the war that he had been overworked. He was seen every two weeks and after three interviews was almost

entirely free of pain, eating well, and gaining weight. He stated that he was feeling much happier in his work. Roentgenological study showed slow but definite healing of the ulcer and at follow up, six months after entering the clinic, he was in good health.

Discussion: It is impossible to say that psychotherapy cured this man, but, if one agrees with Wolf and Wolff that suppressed resentment increases gastric secretion and motility, he may readily believe the improvement in the patient's emotional state removed the precipitating cause for the recurrence and persistence of his ulcer. Certainly he had previously made no improvement on a thorough dietary regime. In spite of the temporary improvement it must be pointed out that no attempt was made to alter his fundamental personality, with its rather paranoid trend, so recurrence is possible. At any rate the improvement in his general health and happiness was very marked.

CONCLUSION

The gastro-intestinal tract is peculiarly prone to be the site of disorders arising from emotional tension. As in any branch of medicine certain patients do not respond easily or at all to treatment but a great deal can be done for many if approach is made in a proper manner. These patients are ill and are earnestly seeking help, though they may not know what sort of help they require. Telling them not to worry and requesting that they stop bothering the doctor is only an admission of inability to handle such illnesses. It should be kept in mind that often much more can be done for patients suffering from these conditions than for those with frankly organic pathology such as malignant disease or liver cirrhosis. Certainly no patient is more grateful and makes a more lasting friend than one to whom the doctor has shown kindness and encouragement during a period of unhappiness.

REFERENCES

- Alvarez, C: Nervousness, Indigestion and Pain. Paul B. Hoeber, Inc., New York, 1943.
Bond, E. D.: Psychiatric Contributions to the Study of the Gastro-Intestinal System. Am. J. Dig. Dis., 5:482, 1938.
English, S. and Weiss, W.: Psychosomatic Medicine. W. B. Saunders

- Co., Philadelphia, 1943.
Ross, T. A.: The Common Neuroses. William Wood and Company, Baltimore, 1937.
Wolf, S. and Wolff, H. B.: Human Gastric Function. Oxford University Press, New York, 1943.

Gastro-Intestinal Symptomatology in Schizophrenia

By

JEROME M. SCHNECK, M.D.*

FORREST HILLS, N. Y.

THE PURPOSE of this paper is to discuss the occurrence of gastro-intestinal complaints in schizophrenic patients. The concepts presented are not directed to the psychiatrist but to the physician seen prior to psychiatric consultation. The apparent predominance of somatic complaints, often gastro-intestinal, results in some cases in disguising the underlying schizophrenic pathology. The gastro-enterologist is, therefore, consulted frequently by schizophrenic patients in whom the mental illness may not be recognized unless possible evidence of a personality disorder is given careful consideration.

CONCEPTS OF SCHIZOPHRENIA

The Kraepelinian conception of schizophrenia, embracing four categorical types (simple, catatonic, hebephrenic, and paranoid) of a chronic disease, the cure of which must contradict the diagnosis, has given way in some psychiatric circles to recognition of diverse forms of symptomatology regarded more optimistically and indicative of a disorder of thought and affect capable of recognition in relatively early stages of development. The term schizophrenia, as a matter of fact, was Bleuler's contribution, appearing some time after wide acceptance of Kraepelin's classification of dementia praecox which in turn developed out of the amalga-

*First Lieutenant, Medical Reserve, United States Army.

mation of Morel's "démence précoce," Hecker's hebephrenia, and Kahlbaum's "katatonie," the descriptions of which appeared in 1857, 1871 and 1874, respectively (1). Freud's introduction of a much needed dynamic psychology into psychiatry, Adolf Meyer's work on the life study of patients with mental illness, and Hoch's description of the "shut-in" personality, have contributed immensely to an understanding of schizophrenia which is still widely diagnosed, nevertheless, according to Kraepelin's four main types (2). Researches in this disease as a functional rather than an organic entity have been progressing, however, and more recently the descriptive terms of schizophrenic personality, pre-schizophrenia, incipient schizophrenia, and ambulatory schizophrenia, have made their appearance in the writings of dynamically rather than descriptively oriented psychiatrists. These studies and new ideas obviate the necessity, in diagnosing schizophrenia, of seeking mutism, stereotypy, grotesque catatonic postures, hallucinations, gross delusions, and markedly bizarre behavior in order to recognize the schizophrenic illness. Finer and more subtle indications of disease may be detected and the illness discovered and treated early.

Detection of early stages of schizophrenic pathology is, however, difficult at times. Often such patients must be interviewed on several occasions before a diagnosis can be established, and at times only prolonged hospitalization permits sufficient acquaintance with finer defects of thought, emotion, and action to allow for accurate diagnosis. With such patients psychological tests for detecting schizophrenic pathology are frequently helpful (3). Obviously a detailed evaluation of diagnostic features in such patients is beyond the scope of this paper but several of these may be enumerated. They may be observed during conversation with patients while examination procedures are progressing. Should suspicions be aroused, the data may be amplified by information obtained from relatives or friends and psychiatric consultation may then be sought.

Schizophrenia is most easily detected when the patient himself is permitted to speak. At the beginning of the interview the examiner should question the patient as little as possible in order to detect the trend of thought and affect through the patient's communications. Possible indications of schizophrenic pathology may be listed as follows: impaired accessibility; mild indications of negativistic behavior; mild degrees of inattentiveness; vagueness in discussing complaints; inconsistencies in the history with little or no apparent concern on the part of the patient when they are called to his attention; circumstantiality; rambling; introduction of irrelevant data not recognized as such by the patient, followed by spontaneous return to the main stream of conversation; inclusion of words or phrases in conversation having no apparent connection with the main topic under discussion but which need not be grossly peculiar; apparently inappropriate smiling during conversations with inability of the patient to explain the reason, or denial of the fact, or a claim by the patient that he himself had not noticed himself smiling; depression usually in the absence of self-blame and self-depreciatory ideas; apathy; objective evidence of

anxiety which may be of the "free-floating" type although at times related by the patient to specific events; obsessive preoccupation with somatic complaints, frequently gastro-intestinal; elaboration of vague somatic complaints or magnification of the significance of bodily sensations normally experienced; insistence on the existence of somatic disease unwarranted by available facts and findings; impaired concentration or comprehension; a tendency to generalize vaguely when questioned about concrete matters; conversely, an inability to comprehend abstract ideas in every-day usage with a substitution by the patient of concrete data inappropriate in the interview situation; impaired judgment; suspiciousness; misinterpretations difficult to reconcile in the interview situation; queeresses; facial grimaces; obsessional sexual preoccupations.

Few or many of these symptoms may be encountered in schizophrenia. If the findings are numerous it favors, although it is not absolutely indicative of, an illness which has progressed beyond an early stage. Division of these signs and symptoms into groups which are more likely to be found in the various forms of schizophrenia will not be discussed in this report. Neither will an attempt be made to discuss additional signs and symptoms more apt to be recognized and elicited during the psychiatric consultation. The latter involve abnormal impressions which the patient may have of himself and others, pathological interpersonal relationships, dereistic thinking, perceptual distortions, etc.

SIMULATION OF NEUROSES

Some signs and symptoms in schizophrenia may simulate those occurring in the neuroses. Among such findings are anxiety, fatigue, preoccupation with excretory functions, and preoccupation with vague somatic sensations. Often the gastro-intestinal tract is the focus of attention and concern. The neuroses simulated may include anxiety states, some forms of hysteria, neurasthenia, hypochondriasis and obsessive-compulsive neuroses. The likelihood of a neurosis simulating schizophrenia is uncommon but not infrequently schizophrenia "masquerades" as a neurosis. As a result, when gastro-intestinal symptomatology is such as to warrant evaluation of possible psychogenic components, the possibility of the existence of schizophrenic pathology should be given serious consideration.

GASTRO-INTESTINAL SYMPTOMATOLOGY

Gastro-intestinal symptoms in schizophrenic patients may be grouped roughly into two categories: 1) Well-defined symptoms; and 2) Poorly-defined symptoms. The adjective, "well-defined," as employed in this paper, does not refer to appropriate use of simple terms such as nausea, belching, or diarrhea, but rather to a group of symptoms which suggest to the physician one or more definite diagnostic possibilities. This may involve, for example, a group of symptoms suggestive of appendicitis, gastric or duodenal ulcer, or carcinoma of a particular portion of the gastro-intestinal tract. The term "poorly-defined," on the other hand, denotes symptoms which tend to be puzzling, especially when

findings or absence of findings on physical examination tend only to confuse.

Complaints referable to the gastro-intestinal tract in schizophrenics may be as well-defined or poorly-defined as those in any other patient with or without an emotional illness. To list all types of symptoms would, therefore, be unreasonable and unnecessary; a few examples as follows, should suffice: indigestion, heartburn, belching, nausea, vomiting, stomach ache, burning of the stomach, bloating, gurgling sounds in the abdomen, sticking sensations, pressure sensations, constipation, diarrhea, pressure sensations in the rectum, pains localized to a specific abdominal quadrant, generalized abdominal pain, etc. The patient may say, "I think I have appendicitis," or "I have appendicitis," or "I have a stomach ulcer," etc.

The following classification of gastro-intestinal symptoms in schizophrenic patients is suggested: 1) Poorly-defined complaints symptomatic of schizophrenia; 2) Poorly-defined complaints unrelated to underlying schizophrenic pathology; 3) Well-defined complaints symptomatic of schizophrenia; 4) Well-defined complaints unrelated to underlying schizophrenic pathology. Each of these groups may be modified by two subdivisions as follows: a) evidence of organic disease obtained on examination; and b) no evidence of organic disease obtained on examination.

With poorly-defined complaints symptomatic of schizophrenia the absence of organic illness should be more or less expected. Presence of organic illness in patients with complaints symptomatic of schizophrenia would constitute an incidental finding and as such would not, of course, nullify the diagnosis of mental illness. With poorly-defined complaints unrelated to underlying schizophrenic pathology organic illness may or may not be discovered. If evidence for organic illness is discovered this need be interpreted as no more unusual than similar findings on examination for vague complaints in any psychologically well-integrated patient. If no evidence is found for organic disease there would be no reason to insist on the complaints being necessarily symptomatic of the mental illness. The difficulties reflect the current medical limitations in diagnosis rather than the inability of the patient to verbalize his complaints satisfactorily. When well-defined complaints occur unrelated to underlying schizophrenic pathology with discovery of organic illness on examination the co-existent schizophrenia may not be recognized unless the behavior of the patient is sufficiently abnormal to attract attention or the physician is acquainted with more subtle indications of schizophrenic behavior. If, in this group of patients, evidence of organic illness is lacking, the deficiency, as mentioned previously, lies with medical diagnosis rather than inability of the patient to verbalize his difficulties or to cooperate in examinational procedures. The occurrence of well-defined complaints symptomatic of schizophrenia is probably rare and as such may be quite misleading. Evidence of organic illness aside from the history may be absent, with confusion resulting. Should evidence of organic disease compatible

with the nature of the complaints be discovered, the underlying schizophrenia may again remain unrecognized unless thought and affect disturbances are noted.

THERAPEUTIC & PROGNOSTIC IMPLICATIONS

In schizophrenia with gastro-intestinal manifestations the mental illness is of primary importance and the somatic symptomatology of secondary concern except in the case of symptoms suggesting a surgical emergency. Organic illness in a schizophrenic patient requires essentially the same medical care as in a patient who is not schizophrenic. Psychological factors inherent in the relationship between doctor and patient play a role during the course of treatment; their diversity precludes adequate presentation. Much concerning this doctor-patient relationship is not known as is the inter-play between psychic and secondary somatic elements in schizophrenia. Without further amplification it may be stated that improvement in schizophrenic illnesses has been observed during the course of incidental somatic disease in the form of infection, for example, with relapse following recovery from the somatic illness. The physiology and psychodynamics involved have not been fathomed as yet.

When more than one therapeutic approach to a somatic illness is possible in a schizophrenic, psychiatric advice may be desirable especially if surgical interference is considered. Not infrequently medical and surgical manipulations have an unconscious significance for the patient, understood only through thorough knowledge of the patient's psychological status. The trauma which might possibly result need not necessarily be immediately discernible, but it may have far reaching effects in connection with the patient's mental health. Interpretations made by patients of gastro-intestinal symptoms and therapy directed toward the gastro-intestinal tract often relate to experiences, training, and traumata of very early childhood. The effect of treatment in such patients is not the same as that in normal adults.

In treating schizophrenic patients with somatic symptomatology secondary to the mental illness the danger exists of acceding to the unconscious needs of the patient for the therapy employed, without relief and without ultimate benefit to the patient. This may remain unrecognized unless evaluated psychiatrically. Relief of symptoms may possibly result at times because of psychological features inherent in the relationship between doctor and patient and these too may remain unrecognized. The underlying illness would, of course, persist and find expression through other channels.

The therapeutic and prognostic implications, thus, are several. The physician should be aware of the existence of the mental illness. He should realize that his ministrations have psychological repercussions and he should know that the somatic symptoms are secondary. If they alone are treated only part of the problem will have been attacked. The physician should be aware of the fact that unconscious mechanisms may play a role in the patient's search for, acceptance of, and response

to treatment. The possibility of exacerbation of the illness must be considered and the need for psychiatric guidance realized. Unnecessary surgical procedures must be avoided and the possible effects of surgical procedures properly evaluated. Psychiatric advice in managing such problems in schizophrenic patients with gastro-intestinal symptoms is especially important in view of the significance of gastro-intestinal functions in psychological development during infancy and childhood and the role of early experiences in motivating behavior of adults.

SUMMARY

Gastro-intestinal symptomatology in schizophrenia merits consideration because of diagnostic problems relative to co-existent organic illness and schizophrenic pathology. A classification of schizophrenia with concurrent gastro-intestinal symptomatology has been suggested on the basis of well- or poorly-defined complaints symptomatic of schizophrenia or appearing in schizophrenic patients but essentially unrelated to the under-

lying psychopathology. The similarity of gastro-intestinal complaints in schizophrenic patients and non-schizophrenics has been alluded to and it has been stressed that schizophrenia not infrequently masquerades as various neuroses owing to some similarities in symptoms. The development of concepts of schizophrenia as a disease entity has been outlined and signs and symptoms which may possibly be found during interviews with schizophrenic patients have been presented. Therapeutic and prognostic implications relative to the gastro-intestinal complaints and the schizophrenic disorder have been discussed.

CONCLUSIONS

Schizophrenia is a prevalent form of mental illness and gastro-intestinal symptomatology in relation to this illness is frequently encountered. Recognition of the personality disorder is important in order to effect a scientifically oriented therapeutic approach aimed not only at treatment of symptoms but involving the personality as a whole.

REFERENCES

1. Muncie, W.: *Psychobiology and Psychiatry*. C. V. Mosby Company, St. Louis, 1939.
2. *Statistical Manual for the Use of Hospitals for Mental Diseases*. National Committee for Mental Hygiene, New York, Tenth Edition, 1942.
3. Rapaport, D., with the collaboration of Gill, M. and Schafer, R.: *Diagnostic Psychological Testing*, two volumes, Year Book Publishers, Inc., Chicago, 1945.

Peptic Ulcer

A ROENTGENOLOGICAL, LABORATORY, AND CLINICAL FOLLOW-UP OF 200 PEPTIC ULCERS

By

A. J. DELARIO, M.D.*
PATERSON, NEW JERSEY

FROM A REVIEW of articles by Muller, Hingston, and Bergsma, on the incidence of peptic ulcer in various parts of the world, an idea may be gained of the many variations in its form, and the vast extent of its distribution.

The incidence of ulcer as determined by admissions to hospitals, is about 1% in United States, England, France and Germany. Russia has a hospital incidence of .8%, and Italy less than this. In these nations the duodenal ulcer forms from 80 to 90% of all ulcers. In countries in which the people are known to be heavy eaters, the ulcer incidence is higher. It is 16.7% in Denmark, and 5 to 13.5% in Australia, depending upon whether the hospitals were nearer to the equator or in the colder parts of the country. In hotter west Australia, it was 5%; in Tasmania, 13.5%.

That a warmer climate apparently affects ulcer incidence is also shown by the fact that the ulcer incidence among white people that have gone to work for the United Fruit Company in the south is 0.12%, and in these the gastric ulcer is twice as common as the duodenal. Is this lowering of ulcer incidence due to a

change for the better so far as rest, nervous strain, and tension, is concerned, or has it to do with some chemical change in the stomach content? As perspiration occurs, with accompanying loss of acid salts and chlorine content, the alkalinity of the blood increases and the hydrochloric acid content of the stomach decreases. Certainly this is true until complete acclimatization occurs. Some say that the lowered ulcer incidence is caused by heat alone, or by ultra-violet ray, or by the increased vitamin content of food.

It has been definitely shown that heat diathermy applications to the abdomen, or other physical therapy methods may occasionally relieve the patient, but definite cures are hard to illustrate. Theoretically vitamins B and C protect the mucous membrane of the gastro-intestinal tract, but the results of this treatment have not been convincing. That colder weather also activates resting ulcers is shown by Einhorn, who believes that the higher recurrence of peptic ulcers in cold weather is due to respiratory infections lowering the body resistance. He found,

42% recurrence in the fall months,
35% recurrence in the spring months,
19% recurrence in the winter months,
4% recurrence in the summer months.

*Radiologist, St. Joseph Hospital, Paterson, N. J.
Submitted January 7, 1946.

While it is probably true that a warm climate lowers the incidence of peptic ulcer, this may be offset by certain diet characteristics of the population.

For instance, the Abyssinians eat all their food with an almost 100% peppery sauce, which will blister even the mouth in the eating. Peptic ulcer is very common among the Abyssinians. The ulcers are very large, for the most part gastric, and form indurating masses resembling carcinoma. Practically all the ulcers produce obstruction.

The Koreans eat a hot peppery food, and drink much alcohol. They have an ulcer incidence of 5%. The Chinese drink almost boiling hot tea, and have an ulcer incidence of 3%. The ulcers among the Chinese are apt to perforate and hemorrhage, and the mortality from these accidents is very high.

It can therefore be seen that many external factors determine the incidence of ulcers, their position, size, form and extent; whether the accident of perforation or hemorrhage will occur, and the mortality. These factors are climate, food and the stress and strain of the struggle for existence.

There are also internal or hereditary factors. It is well known that individuals inherit certain tendencies or weaknesses in the various systems which under proper external conditions or stimuli make themselves manifested. The weakness, so far as peptic ulcer is concerned, is usually associated with a hyposthenic type of body in which the stomach is low and hypotonic. This type of stomach allows for greater accumulation of hydrochloric acid and prevents, to a great extent, bile, pancreatic and intestinal juices from regurgitating into the stomach to neutralize the acid.

This low, dragging type of stomach probably also causes mechanical interference in the blood supply to the pyloric end of the stomach and duodenum, especially along the lesser curvature, and thus affects the nutrition of the various alkali-supplying glands such as the goblet cells in the antrum and the Brunner's glands in the duodenum, and which also affects the thickness and the condition of the mucous membrane in this area.

Hyposthenic individuals usually also have an unstable autonomic system, which is easily thrown out of balance. Thus changes in the secretory and muscular action of the stomach and duodenum or in its blood supply may bring about the right set of conditions for the formation of a peptic ulcer.

In the light of these facts, it would be interesting to analyze the cases which occurred in our hospital. In the stomach clinic of St. Joseph Hospital, we have studied the results of treatment of 200 peptic ulcers in 185 individuals. There were:

- 19 gastric ulcers
- 156 duodenal ulcers
- 14 parapyloric ulcers
- 11 gastro-jejunal ulcers

The figures as to Race, Sex, Body Type and Age are as follows:

Race

Irish	43	Syrian	3
Italian	35	French	2
American or English	34	Lithuanian	2
Jewish	18	Turkish	1
Holland	18	Assyrian	1
German	15	Greek	1
Polish	7	Swedish	1
Negro	3	Hungarian	1

Sex

Male, 153; Female, 32: a ratio of 5 men to 1 female.

Body Type

76.2% of our patients were of the hyposthenic type.

19.0% of our patients were of the sthenic type.

4.8% of our patients were of the hypersthenic type.

182 were white, 3 were colored.

Age

The ulcers occurred almost entirely during the period of greatest strain and responsibility, the decades being represented as follows:

Decade	Number of cases
10-19	13
20-29	44
30-39	63
40-49	45
50-59	13
60-69	7

The Acidity Factor

A factor which is often cited as of importance, directly or indirectly, in the etiology of peptic ulcer, is an increased amount of hydrochloric acid. The relationship of hydrochloric acid to the formation of peptic ulcers has been demonstrated often in cases of peptic ulcer occurring in Meckel's diverticula and jejunal ulcers following gastro-jejunostomies. Abnormally high amounts of hydrochloric acid may erode normal areas, and it is even possible that smaller than normal amounts of hydrochloric acid may erode areas of deficient nutrition, due to organic or functional narrowing of the blood vessels. I know of no one who has reported a case of peptic ulcer occurring in pernicious anemia, in which no hydrochloric acid is present.

The following figures will show how our group of patients stood as to hydrochloric acid acidity:

- 6 cases showed anacidity consistently (these cases would probably secrete hydrochloric acid under histamine stimulation)
- 9 cases showed subacidity consistently
- 16 cases were consistently normal
- 82 cases were consistently hyperacid
- 72 cases were variable.

Of the 452 Ewald Test meals:

- 23 test meals showed anacidity
- 71 test meals showed subacidity
- 82 test meals showed normal acidity
- 276 test meals showed increased acidity.

Therefore, more than half of the test meals showed increased acidity. It seems best, at this point, to show what happens to an ulcer when the hydrochloric acid values decrease, remain the same, or increase. The figures give the percentage of patients in whom the acidity at a follow-up test meal was lower, the same, or

higher, than in their previous tests at the height of the disease:

Patients whose —	ulcers		
	healed	were not active	continued active
Lower Hydrochloric acid	70%	60%	8.4%
Same Hydrochloric acid	20%	25%	16.6%
Increased Hydrochloric acid	10%	15%	75.0%

These figures tend to confirm the finding that as the hydrochloric acid decreases the ulcer improves and heals, and as the hydrochloric acid increases the ulcer gets worse.

Etiology of Pain in Peptic Ulcer

It is of value, in the treatment of these cases, to discover what causes pain, the most important symptom in peptic ulcer. There are two theories as to the method of production of pain in peptic ulcer, first, that the increased production of hydrochloric acid irritates the nerves in the ulcer, and second, the mechanical theory, which will later be explained.

Against the theory of increased hydrochloric acid as the cause of pain, we have found:

1. Six cases of anacidity, and 9 cases of subacidity, which maintained these conditions consistently. We had 72 cases, which, although they usually showed increased hydrochloric acid, at some one time in the various examinations, showed a decreased amount, the pain remaining the same.
2. In some cases administration by mouth of hydrochloric acid actually relieved symptoms, and it has been shown that the application of hydrochloric acid directly to the ulcer, under local anesthesia, did not cause pain.
3. In some patients symptoms disappeared only when the amount of hydrochloric acid in the stomach increased, and it was only when the acidity reached its highest point that the roentgen defect disappeared.
4. Many people believe that the administration of alkalis relieves pain because the acidity is reduced, but many other factors which have no apparent effect upon the acidity cause the pain to disappear, as in one of our cases pain was relieved at one time or another by rectal dilatation, laxatives, powders, pills, drops, morphine soft, hard, or liquid diet, lavage, tube treatment, removal of teeth, abdominal operation, et cetera.

The theory most widely accepted is that pain has to do with the mechanics of the stomach, and is produced in the same way as, normally, hunger pains are produced; that is, by over-activity and increased tonicity of the muscles of the stomach. The only sensory end-organs the stomach has are those which respond to the stimulation of pulling. It has no sense organs, as the skin, which give a painful sensation by pinching, cutting, clamping, burning, et cetera. This theory explains how the gallbladder and appendix may give symptoms like those of an ulcer, reflexly by increasing the muscular activity of the stomach.

Against the mechanical theory of pain: in a great many cases peristalsis was hardly seen, especially in long-obstructed cases, and yet these patients had as much pain as those cases which had a great deal of muscular activity. In fact, in these cases, as the obstruction disappeared, and the patient became symptom-free, the tone and peristalsis of the stomach increased. In many cases the patients were symptom-free at one time, or in great pain at another time, with the same amount of tone, the same number and depth of peristalsis.

I believe that it is not enough to have merely an increased tonicity and peristalsis of the stomach to cause pain, but it is necessary that the base of the ulcer be attached to the muscle of the submucosa or the muscle coat proper. Normally the mucous membrane slides inside the stomach and duodenum, and unless the ulcer is attached to the muscle, no tension can be made upon it by the muscular activity.

The ulcer can be attached to the muscle either by adhesion, by edema or by inflammation. In this way we can explain the cases in which we actually have an increased tone and peristalsis, and yet no pain exists, by assuming that the ulcer is not attached to the muscle coat. It explains also how the same amount of tone and peristalsis may cause a great deal of pain in some patients whose ulcers are attached, and very little in others, whose ulcers have affected the mucosa only. It also explains how a penetrating ulcer, after it has punched a hole in the stomach wall, and has become pocketed off, may be quiescent, for no longer can the group of muscles it has disconnected cause tension upon it.

In evaluating pain in an individual, the nationality, individual peculiarities, different states of rest or fatigue, the state of the nervous system, the proper assimilation of calcium and potassium, and environmental conditions must be kept in mind. Any of these conditions may make the mechanics of the gastrointestinal tract more delicately balanced.

Number of Operations

It is interesting to note how many operations were performed on this group of 185 patients.

In all, there were 72 operations, as follows:

- 15 for perforations (14 before coming to our clinic).
- 26 for gastro-enterostomies (some were done before coming to our clinic).

Of these 26:

- 1 was done for persistent pain.
- 14 were done for ulcers with obstruction.
- 11 were done for non-obstructive ulcers.
- 3 gastric resections were done.
- 4 pyloroplasties.
- 3 operations for unhitching the previous gastro-enterostomies.

21 miscellaneous operations.

Of these 21, there were:

- 11 appendectomies.
- 3 adhesions.
- 2 hernias.
- 2 laparotomies.
- 2 cholecystectomies.
- 1 salpingectomy.

Results of Treatment

It is very important, in the evaluation of results, to be sure that the patient treated actually had an ulcer. It is not always easy to make an accurate diagnosis of a duodenal ulcer. In 20 cases, or 10% of the total, there was a clinical history of a peptic ulcer; the x-ray examination showed a defective cap; some even had a six-hour gastric residue, and an increase in the acidity of the stomach content. These 20, in later x-ray examinations, showed a normal stomach and duodenum, but certain symptoms remained, and only by repeated Roentgen examinations, by surgical, or autopsy findings, were finally diagnosed as:

Peritoneal adhesions	6
Chronic cholecystitis	4
Cholelithiasis	3
Chronic appendicitis	2
Brain tumor	2
High blood pressure	1
Right inguinal hernia	1
Neurasthenia	1

Had it not been that these patients were under the personal supervision of the same doctors during the whole course of their treatment, these 20 cases might easily have been recorded as cured peptic ulcers.

In evaluating the results of the different types of treatment it must be kept in mind that no clear cut line can be drawn between the various treatments, since most of the patients had more than one type, and second, that the length of time the ulcer had existed, the length of time of treatment, and the position of the ulcer greatly influenced the results.

In our cases the length of time symptoms existed is summarized in the following table:

Total Length of Time Symptoms Existed in All Cases		Years
A. Before first roentgenogram was taken.		
1. Average number of years of prodromal symptoms		4.04
a. Number that had prodromal symptoms		
b. Number that did not have prodromal symptoms	45	
c. Unascertained	36	
2. Average number of years of pain (beginning of attachment of ulcer to underlying muscle)	4.3	
a. Number that had pain	169	
b. Number that never complained of pain	5	
c. Unascertained	11	
3. Average length of time symptoms existed before first roentgenogram	8.34	
B. After the first roentgenogram was taken		
1. Average length of time symptoms existed after first roentgenogram until the patient was well, or if ill, until end of study.		
Total length of time symptoms existed, average	12.24	

It will be interesting to state here how long these cases were followed up by clinical, laboratory, and x-ray examinations:

26 were followed for 1 year,
83 were followed for 2 years,
18 were followed for 3 years,
12 were followed for 4 years,
16 were followed for 5 years,
4 were followed for 6 years,

13 were followed for 7 years,
13 were followed for 8 years, plus.

From the following figures, it can be seen that those patients whose ulcers improved had had symptoms, on the average, a shorter time than those whose ulcers did not improve:

Length of Time Symptoms Existed before Treatment Started

	Type of Treatment		
	Duodenal Intubation	Bed rest, Sippy diet	Ambulatory, Bland diet
Patients whose ulcers healed:			
Shortest time	3 weeks	3 weeks	3 weeks
Longest time	20 years	25 years	26 years
Average time	4.25 years	5 years	3.5 years
Patients whose ulcers did not heal:			
Shortest time	1.5 weeks	6 weeks	1.5 weeks
Longest time	18 years	13 years	31 years
Average time	9.2 years	8 years	8.8 years

It is interesting to note here that the average age of the incidence of the ulcer in those who improved was 37.8 years, while in those who did not improve it was 30.6 years. Thus, the younger the patient is when he develops an ulcer, the harder it will be to cure it.

The length of time it took for an ulcer to heal under constant treatment of one type or another averaged 16 months, the shortest time was 2 months, the longest time was forty months.

This of course, does not mean that a patient has had a duodenal tube in him for 16 months. It does mean that the patient started his treatment with a duodenal tube for 3 to 6 weeks, and later went on a liquid, soft solid, or modified diet until the ulcer disappeared, as evidenced by x-ray. A gastric ulcer may heal, but only rarely does a duodenal ulcer disappear during the course of a duodenal tube treatment. This occurs only in an early ulcer, of one to three weeks' duration, which is not calloused, and which may present no definite niche by x-ray.

The only x-ray signs of an ulcer in this stage are the secondary signs, such as increased tone and peristalsis in the stomach, and an irritable and defective cap. There may be pain and slight tenderness, over the duodenum and an increase in hydrochloric acid in the stomach. A calloused ulcer takes a long time to heal. Some have been found, during the course of an operation for some other lesion, to be healed after 6 to 12 months of dieting. Even after a gastro-enterostomy 3 to 6 months may be necessary before healing takes place, in a calloused ulcer. Of course, it must be remembered that the patient is not suffering pain during this treatment time.

Gastric Ulcers

In this series there were 19 gastric ulcers. Nine of these gastric ulcers occurred in patients who were being treated for duodenal ulcers.

8 gastric ulcers occurred in women. All were cured as evidenced clinically and by x-ray examination.

4 of these women were treated with duodenal tube and hospitalization.

- 2 were treated with Sippy diet, and hospitalization.
- 2 were ambulatory treated with soft solid diet.
- 11 gastric ulcers occurred in males. Seven were cured.
- 3 were cured with duodenal tube and hospitalization.
- 2 were cured with Sippy diet and hospitalization.
- 2 were cured with gastro-enterostomy.
- 2 patients died as a result of surgical intervention.
- 2 patients are unheard from.

While in duodenal ulcers the treatments must be prolonged for months to obtain a cure, in gastric ulcers a cure usually occurs in 4 to 8 weeks by medical measures. It takes 2 to 4 weeks for a gastric niche to disappear after a gastro-enterostomy. If the patient has had symptoms for a long time it may take 8 to 12 months of continued medical treatment and dieting before the niche disappears. In one woman who had had symptoms for 20 years, the ulcer healed and broke down three times before it remained definitely cured.

No matter how long the ulcer has existed, or what its position, the fact that the patient has been competently treated reduces the chance of perforation, of the necessity of having an operation, and the mortality.

Twenty-eight per cent of the cases which were haphazardly treated, perforated, died or required surgical intervention, whereas only 2.7% of the patients who had been competently treated met with these accidents.

The following figures show the number of cases in which the symptoms were improved, or cured under the different types of treatment:

Duodenal tube treatment and hospitalization	86%
Sippy diet treatment and hospitalization	46%
Ambulatory plus diet	60%

But on the bases of symptoms any type of treatment will give a cure at some time, since in most cases the ulcer becomes dormant and the symptoms disappear for a while regardless of treatment. If, however, the Roentgen findings are considered with the symptoms, the figures become significant, and read as follows:

Type of Treatment	Improvement shown by x-ray	Healing shown by x-ray
Duodenal tube treatment and hospitalization	62%	39%
Sippy treatment and hospitalization	37%	27%
Ambulatory plus diet	35%	21%

In a series of 7,700 autopsies performed at Bellevue Hospital, Sturtevant and Shapiro found that 20% of ulcers in the stomach or duodenum were healed. This group may or may not have been treated during life. Our figures, because of treatment, are higher.

Those who did not improve may still have a chance to do so, because very often a second intubation or Sippy diet may be necessary to effect a cure. Also, these lesions which are cured may still break down again, as occasionally happens.

It is evident that a 39% cure by the tube treatment is not a very successful method of treatment in peptic ulcers. But our cases were very long existing ulcers, and with more prompt diagnosis and a quicker application of the tube method of treatment, if possible, with five or six weeks' rest in bed, and with a long

diet regimen afterwards, lasting from six months to one year, or until the roentgen examinations are negative for active lesion, I believe that the figure can be raised.

Surgery in the Treatment of Peptic Ulcers

Our results indicate that surgery should not be attempted in the treatment of gastric ulcers. As for the fear that such an ulcer may turn into a carcinoma, I cite Brown's experience in 77 cases of gastric ulcer, only one of which died of carcinoma, and in this case there was the healed scar of an ulcer near the carcinoma.

Most ulcers seen along the lesser curvature of the stomach in the pars media and above can be identified roentgenologically rather accurately to be either benign or malignant. Most ulcerations in the prepyloric area can also be accurately diagnosed as benign or malignant. In about 10% of these prepyloric ulcerations, the diagnosis as to benign or malignant is difficult to make. It is difficult in these cases to make the diagnosis even at the operating table. The pathological diagnosis turns out to be in about equal proportions, benign ulcers, malignant ulcers and malignant degeneration in benign ulcers.

Surgery should be resorted to only in the case of accidents resulting from the ulcer, such as perforations, or perforating lesions, possibly in some cases of persistent pain unrelieved by medical measures, and possibly occasionally in repeated hemorrhage.

Perforations

In the past seven years there have been admitted to our hospital 797 cases of peptic ulcers. In the same time 90 cases of perforations have been admitted, or about 11%. More than two-thirds of the perforating ulcers were gastric ulcers.

In an effort to determine what relationship exists between perforation and the activation of ulcers, a study was made based on these figures, showing the relation of perforations to the periods of the year when dormant ulcers became activated. It should be noted that ulcers tend to perforate about two months after they become activated. Whereas ulcers become active and produce symptoms in January, May and October, ulcers tend to perforate in March, August and November.

By another study showing the frequency of perforations in older patients and in chronic cases, it was shown that the older the patient is, and the longer he has had his ulcer, the more apt he is to have a perforation.

I have been especially interested to know why peptic ulcers recur after the suturing of a perforated lesion. Lewisohn says that in 33 cases of perforating peptic lesions, 20 were well after operation, which included a simple closure in 10, simple closure plus gastroenterostomy in 10 others. The remaining 13 were still sick. Grave says, "It cannot be denied that more than one-half of the patients subjected to simple closure after

perforation remain completely cured."

We had 15 perforations, of which 3 patients died from the perforation and 1 lived without an operation, but in the other 11 cases symptoms of an ulcer returned. Two had to have pyloroplasty done later, 3 needed a gastroenterostomy, and six still have trouble. The roentgenograms showed the same lesion after suture as before.

I believe that the methods of suturing are wrong. In hasty effort to save the patient's life the edges of the ulcer are sutured so that it is actually reconstructed. The necrotic edges of the ulcer ought to be excised, if possible, before suturing.

Obstruction

Out of 185 cases of peptic ulcer, 61 were obstructed:

- 11 had a 24 hour retention (when there is 90% six hour retention, a 24 hour obstruction is likely to occur).
- 23 had 50% or more six hour retention.
- 13 had 25% six hour retention.
- 14 had a 10% to 25% six hour retention.

There were three causes for six hour residue in our cases:

1. Spasm of the pylorus, direct or reflex.
2. Edema and inflammation about the ulcers near the pylorus.
3. Scar tissue or adhesions near the pylorus.

Spasm usually occurs in all cases of peptic ulcer. This spasm at the pylorus is due to direct irritation by the ulcer when it is situated near the pylorus, or reflexly, when further away. It can be seen at the beginning of the examination, lasting ten minutes to one hour or more. In spite of this spasm, most ulcer patients do not have obstruction, because of the increased tone and peristalsis of the stomach which accompanies ulcers, but if the ulcer is of such a nature, or is so situated as to prolong the spasm, it may cause a five hour residue in the stomach.

Edema and Inflammation about the ulcer can exist independent of, or associated with, spasm, and when near the pylorus, one or two inches of the pyloric end of the stomach may not fill. Some barium can be forced into the cap after a long period.

Scar tissue or adhesions: When, in the course of healing, an ulcer at or near the pylorus contracts and causes the canal to become smaller, or adhesions forming in the peritoneum on contracting narrow the canal, there will come a time when increasing hypertrophy, tone and peristalsis of the stomach cannot overcome this contraction, and obstruction will then persist. In these cases the stomach will fill right down to the contractions, and it is usually large, dilated, and low. A small stream can be seen trickling through the narrow area. The cap is contracted and small, and is much less tender than in the cases due to spasm and inflammation.

Some of our cases presented interesting facts. One patient had a large residue at both five hour and twenty-four hour examinations. On liquid diet, which usually causes patients to stop vomiting and gain weight, this patient made no improvement, and was still obstructed. A tube was passed, the sinker never

leaving the stomach, and the patient was given the same liquid diet through the tube. After three weeks of this treatment his obstruction disappeared, and he was free from pain.

In this case the deciding factor must have been physical and mental rest, because the tube treatment was given at the hospital, whereas the patient had been an ambulatory case when taking the diet. In three other cases the usual liquid diet with milk failed to relieve the pain and vomiting, which were relieved, however, when the patient was placed on a soft solid diet, consisting of oatmeal, rice, milk and bread.

Three of our patients have been continually obstructed for over five years, but feel fine. Thus it seems that although a stomach may be obstructed to a barium meal, which is a heavy mixture, it may function in some cases with a liquid diet, and in other cases with a soft solid diet. Though there is an obstruction to barium, these patients can go on apparently in good health if they adhere to a modified diet. This is one argument that medical men have against surgery in obstruction. The reverse of this is also true at times, that is, even though the stomach may not be obstructed to a barium meal, obstruction is shown when a stomach tube is passed. Twenty-four hours after his last meal one patient still had a pint of fluid in the stomach, with spinach eaten thirty-six hours previously. One patient was obstructed for five years. On becoming pregnant her obstruction disappeared and she has remained well for four years. She still has a lot of scarring about the pylorus, but no ulcer niche or obstruction.

Ulcers producing the most obstruction occur in the pylorus in the parapylic region, and these cases remain obstructed the longest. There were fourteen of these ulcers. Nine of our gastric ulcers produced obstruction, and there were 38 cases of obstruction with duodenal ulcers. The obstructed cases had been sick only a trifle longer than the non-obstructed cases:

The average length of time patients with obstruction were ill before first x-ray:

Prodromal symptoms	4 years
Pain symptoms	5.7 years
Total	9.7 years
Average length of time since first x-ray	3.3 years
Total length of time patients with obstruction were ill, average	13 years

Until this study was made I had been under the impression that obstruction was an indication for surgery, but this is not the case. Just as many patients having obstruction are cured as those who do not have obstruction and those with obstruction get well just as rapidly. Under proper treatment the spasm disappears, the edema and inflammation accompanying the ulcer get better, and with the removal of these the stomach can empty itself in six hours, even though a lot of scarring exists.

Results of Treatment of Obstructed Cases

It must be remembered that 9 cases of obstruction,

or 14.7%, occurred with gastric ulcers, and gastric ulcers heal easily, as I have shown. This would naturally better our results. It is interesting to note that 14 cases of simple ulcers became obstructed while they were on an ambulatory diet treatment.

Results of Treatment of Obstructed Cases

10 cases, or 16.4% of the obstructed cases have no symptoms, or occasional symptoms; X-rays are normal.

Of these,

- 1 case had had 24 hour obstruction,
- 4 cases had had 50% six hour obstruction
- 2 cases had had 25% six hour obstruction
- 3 cases had had 10% six hour obstruction.

These cases were followed by x-ray for an average of 4.3 years.

- 6 were treated with duodenal tube and hospitalization,
- 4 were treated with ambulatory diet.

15 cases, or 24.5% of patients have occasional symptoms, not typical of an ulcer; x-rays show healed ulcer with scarring.

Of these,

- 3 cases had had 24 hour obstruction,
- 4 cases had had 50% six hour obstruction,
- 5 cases had had 25% six hour obstruction,
- 3 cases had had 10% six hour obstruction.

These cases were followed by x-ray for an average of 5 years.

- 8 were treated with duodenal tube and hospitalization.
- 7 were treated with ambulatory diet.

Thus 25 cases or 40.9% of the total obstructed cases were cured of their symptoms, obstruction and ulcer. This is about the same number of cures as obtained in the entire group of simple ulcers without obstruction.

2 cases, or 3.2% have no symptoms, or occasional symptoms (not of an ulcer). X-rays show an ulcer almost completely healed, with no obstruction.

- 1 case had had 24 hour obstruction,
- 1 case had had 50% six hour obstruction.

These cases were followed on an average of 7.2 years by x-ray.

- 1 was treated with duodenal tube and hospitalization.
- 1 was treated with an ambulatory diet.

6 cases, or 9.7% have no symptoms, or occasional symptoms (not of an ulcer). X-rays show a dormant ulcer, yet there is no six hour obstruction.

- 1 case had had 50% six hour obstruction,
- 1 case had had 25% six hour obstruction,
- 4 cases had had 10% six hour obstruction.

These cases were followed on an average of 2.5 years by x-ray.

- 3 cases were treated with duodenal tube and hospitalization.
- 3 cases were treated with ambulatory diet.

24 cases, or 39.3% still have symptoms of an ulcer, and the obstruction still persists. X-rays show the same amount of obstruction, and the same ulcer.

- 5 have 24 hour obstruction,
- 10 have 50% six hour obstruction,
- 5 have 25% six hour obstruction,
- 4 have 10 to 15% six hour obstruction.

These cases were followed by x-ray for an average of 1.8 years.

- 3 were treated with duodenal tube and hospitalization.
- 19 were treated with ambulatory diet.
- 2 were treated with Lorastadin (not by us).

In 4 cases, or 6.5%, the symptoms of ulcer disappeared, but returned. X-rays showed a return of obstruc-

tion, although it disappeared at some time during treatment.

- 1 had had 24 hour obstruction,
- 3 had had 50% six hour obstruction.

These cases were followed by x-ray for an average of 3.25 years.

All were treated with ambulatory diet.

How long does it take for a peptic ulcer obstruction to disappear after treatment?

Of course the length of time that is necessary for a peptic ulcer obstruction to disappear depends upon whether the obstruction is due to spasm, or to actual scar tissue contraction. I have seen some cases with 48 hour gastric obstruction which showed no obstruction after two or three days; in this case the obstruction was obviously due to spasm at the pylorus. Most of the gastric ulcers, especially those situated high up along the lesser curvature show obstruction at the pylorus as a result of spasm. In one patient having 50% six hour residue as the result of gastric ulcer along the lesser curvature of the stomach, about an inch away from the esophagus, the ulcer and the obstruction disappeared for the first time in one month, returned again in a month, and persisted for four months before disappearing for the second time. The patient has now been well for four years.

In another patient with 24 hour obstruction due to a gastric ulcer about the middle of the lesser curvature, the ulcer and the obstruction disappeared in about three months, but returned again later. Then for over six months of constant treatment, with diets, duodenal tube, and hospitalization, the obstruction still existed. When surgery was advised, the patient refused, went on a diet of whey milk, and in four months both the ulcer and obstruction disappeared and have remained away now for over two years.

In duodenal ulcers, also, an obstruction may be the result of the pylorospasm. One patient had 90% twenty-four hour obstruction, with an ulcer history of seven years' duration. His gastric analysis showed a total acidity of 79, free hydrochloric acid, 56 and blood positive. After only two months on a simple diet the cap became normal, the obstruction disappeared, and the test meal showed a total acid of 10, free hydrochloric acid of 0, and blood negative. The patient had been symptomless and negative by x-ray for 3½ years.

When obstruction occurs as a result of edema, inflammation, or scarring in cases of pyloric or parapyloric ulcer, the length of time it takes for the obstruction to disappear may be from six months to four or five years. One patient, Mr. Z., who had a 25% twenty-four hour obstruction, became symptom free as soon as he was placed on a diet. His vomiting disappeared but his obstruction was still present. It took three months for the twenty-four hour obstruction to disappear. At this time the 75% six hour obstruction was reduced to 50% six hour obstruction. At the end of six months the six hour obstruction was reduced to 30%, at the end of 8 months to 25%, and at the end of 15 months the obstruction had disappeared. After a year and a half the pyloric ulcer was healed, but showed

distortion commonly seen as a result of scarring.

Another patient, Mrs. V., had had twenty-four hour obstruction as a result of a pyloric ulcer for four years, although she was on an ambulatory diet. Finally the twenty-four hour obstruction disappeared, but the six hour obstruction continued for another year. Then she became pregnant; her obstruction and her ulcer disappeared, and the patient has been well for four years, but she still has scarring in the parapyloric region as a result of healing of the ulcer.

How long does it take for obstruction to disappear by surgical methods?

It is the common belief that as soon as the patient is operated on for obstruction by gastric resection, or gastro-enterostomy, the obstruction disappears. Of course, this is not the case.

The following is a typical example of how long gastric retention may persist in a properly made gastro-enterostomy:

Mr. P. had a gastric ulcer about the middle of the lesser curvature causing a six hour gastric obstruction. The patient was operated on, gastro-enterostomy was done, and his obstruction symptoms of vomiting, and pain, disappeared almost immediately after the operation. However, an x-ray examination two weeks after operation still showed a gastric ulcer, and the obstruction, although trickles of barium did go through the stoma. Four weeks later the obstruction still existed, but the ulcer was very much smaller. Six weeks later the ulcer was gone, and the obstruction was gone. The test meal at this time showed total acidity, 39, free hydrochloric acid, 20, blood positive. It was only three months later that the total acidity became 16, hydrochloric acid 0, and blood 0.

This spasm of the stoma might be attributed to the ulcer, which still existed, but it might also be the result of the surgical disturbance of the sympathetics which lie in the coats of the stomach and the intestines.

Even when gastric resection is done, the stomach does not empty immediately. There is usually complete gastric retention for the first several days, and some cases have been known in which the resected stomach has kept all its barium for as long as six days (Cocci).

Hemorrhage

In our series of 185 cases there were only 22 hemorrhages. Nine were very severe hemorrhages, in which the patient fainted, became blanched and appeared moribund. Most of these severe hemorrhages occurred in gastric ulcers. None of these 9 patients died, 3 were cured, 1 by means of a duodenal tube, 1 by diet, and one by surgery, 2 are better, and 4 are about the same.

Thirteen showed occult blood by test meal. Of these, six were cured with duodenal tube, 2 were cured with a diet, one was better with a duodenal tube, 2 were the same with a duodenal tube, one was the same with a diet, one was cured with gastroenterostomy. Only two that had previously shown occult blood later developed a severe hemorrhage. However, two that had had no

occult blood at all later suffered a severe hemorrhage.

Fowler and Hurewitz, in 1,046 cases of peptic ulcer, found that hemorrhage occurred in 257, or 24.5% of cases. 21.8% occurred in duodenal ulcers, and 31.8% in gastric ulcers, and 46.6% in gastro-jejunal ulcers. Seventeen out of 257 cases died, or 7%. They answered the question as to whether the patient, having had one severe hemorrhage, is more likely to have another, with the following figures: 126 patients had a single hemorrhage, 46 patients had two hemorrhages, and 23 had three hemorrhages.

It has always been a difficult task to know what to do with a bleeding ulcer. Some say that these patients should not be transfused, as this will increase their blood pressure and their hemorrhage. Some believe that they should not be given opiates, since this will increase the spasm. Practically all of our patients with severe hemorrhage received transfusions and opiates, and have done well.

Hinton believes that the treatment of hemorrhaging ulcers by medical or surgical methods depends upon how the patient is treated before the hemorrhage occurs. In Group I, a group of 87 cases, were 16 who were admitted to the hospital with hemorrhage although they were under competent medical care before the hemorrhage occurred. These ulcers, he said, are usually large, or perforating ulcers. He believes that they should be operated on after the patient has recovered from the effect of the hemorrhage. We had four such cases; 2 recovered completely after operation; 2 recovered completely after medical treatment.

In Hinton's Group II, there were 11 cases in which the hemorrhage occurred months or years following an operation for an acute perforation of a chronic ulcer, although the patient had not hemorrhaged before the operation. Six cases had had a gastroenterostomy, 2 had had a pyloroplasty, one an excision with gastro-enterostomy, one a simple excision, one a partial gastrectomy. No marginal ulcers were found in these cases; the deformity was at the site of the original lesion. He says that it is better to be conservative in these cases, as these cases do not cause recurrent hemorrhages.

In Group III, there were 5 cases of hemorrhages occurring in ulcers that had been previously operated on for hemorrhage. In this group it is hard to know what to do.

In Group IV, there were 17 cases, in which the patient had had a negative or a very short history of gastro-intestinal disease, and then had suddenly had a hemorrhage. Nine of these patients died. The 8 that had recovered were treated conservatively, and no second hemorrhage occurred.

In Group V there were 38 cases in which the patient was admitted with hemorrhage after a long history of ulcer, but without regular medical treatment. Thus it can be seen that untreated cases run a greater chance of bleeding than treated cases. Seventeen of these patients were operated on for their hemorrhages, and 4, or about one-third of them died. Three had a

partial gastrectomy, two pyloroplasty, one local excision, three excision, plus gastroenterostomy, eight had gastroenterostomy. Of the four that died one had had partial gastrectomy, three had had gastroenterostomy. Twenty-one of the 38 cases in this group were treated conservatively, and none developed a second hemorrhage.

Thus it seems that hemorrhages from an ulcer should be treated conservatively, and if operation must be performed in those cases of hemorrhages in older patients in whom you fear bleeding won't stop because of arterial sclerosis or because of some underlying disease such as syphilis, etc., it should be done after the hemorrhage has entirely stopped. It seems better, however, to treat the case medically.

As is apparent in this paper, no place has been found for surgery so far in the treatment of non-perforated peptic ulcer. It should almost never be used on a non-obstructed peptic ulcer. Obstructed peptic ulcers do as well as non-obstructed ulcers under treatment; possibly those that don't do so well could be operated on. It should rarely be resorted to in cases that hemorrhage. Only one patient in all this group of 185 cases had to have an operation because he could no longer stand the pain which had not disappeared with the medical measures after three months. Surgery may be necessary in the treatment of gastrojejunal ulcers, but of course this is a condition which is brought about by surgery itself.

This does not necessarily mean that surgery has not produced results in the treatment of peptic ulcers. Naturally it must be resorted to in cases of perforation. In these cases, if a permanent cure is to be desired, the ulcer edges should be excised.

From a surgical point of view it is sometimes difficult to know whether a pyloroplasty, a gastroenterostomy, or a gastric resection should be done. In our cases of four pyloroplasties performed, 2 are better. Those who got better have a lower hydrochloric acid content in the stomach than they had before the operation. If the hydrochloric acid is not reduced the chances that the patient will get better are not good.

Twenty-six of our cases had a gastroenterostomy. One was done for persistent pain, fourteen for obstruction, eleven for non-obstructive ulcers. Sixteen, or about 61% are feeling fine, but those that were obstructed obtained the greatest benefit. Of those who are feeling fine, one was operated on for persistent pain, thirteen for obstruction, and two were non-obstructed.

Of those who felt worse after the operation, one patient had had an obstructed stomach, and nine had had a non-obstructed stomach. In those who felt worse, usually a gastro-jejunal ulcer or adhesions developed. Eight occurred in our series of 26, or about 30% of the cases.

According to Lahey and Swinton, the range for gastro-jejunal ulcer following gastroenterostomy is 1.7% (Walton) to 24% (Strauss, Block and Friedman). This wide discrepancy may be due to the fact

that some surgeons operate on obstructed ulcers, while others operate on all types of ulcers.

Because of this high incidence of gastro-jejunal ulcer following gastroenterostomy in the treatment of peptic ulcer, the tendency now is to treat peptic ulcer surgically by resection, but according to Lahey, the incidence of peptic ulcer following gastric resection may also vary from .4% (Schwartz) to 10% (Gatewood). Allen believes that marginal ulcers occur as frequently after resection as after gastroenterostomy, and in addition, a secondary operation is more difficult to perform after a resection.

If there is a discrepancy in the figures as to the number of ulcers that appear after a gastric resection or a gastroenterostomy, there can be no argument or question as to the greater mortality which accompanies gastric resection.

Other Methods of Treatment for Peptic Ulcers (Injection Method)

A method of management especially popular in the past several years has been the injection treatment of peptic ulcer, with bacteria, foreign proteins, Synodal, and Lorastidin. We believe that any benefit at all derived by patients under this management is due to the dietary measures which accompany the injections, or is due to a psychic effect. Why should the injection of a small amount of histadine, one of the amino acids absorbed, in the digestion of proteins, in much greater quantities than can be injected, be of any value, if that absorbed during digestion is insufficient to cure the patient?

In only one of our 24 cases (a gastric ulcer) did the ulcer disappear in the course of an injection treatment. It promptly returned again one month later. In the other cases which showed improvement, a dietary regime had to be kept up for several years before results were actually seen.

In our 24 cases, injections, Lorastidin, for the most part, had been given at some time by physicians outside our service, but it has fortunately been possible to follow these cases during their treatment and for some months afterward. The following show the clinical and x-ray findings in our follow-up:

PATIENTS TREATED WITH INJECTIONS

Symptoms gone, or improved. X-rays show a cured ulcer. 4 cases, 16.7%.

2 had to be treated by dietary regime for an average of 3 years after Lorastidin was given before the ulcer healed.

1 case healed, broke down one month later, and required 4 months of dietary regime before it healed permanently.

Symptoms improved. X-ray improved. 6 cases, 25%.

In these cases also the x-ray findings were unchanged after the administration of Lorastidin. These patients had to be hospitalized and given a duodenal tube treatment, and then remain on a diet for an average of 3.2 years. The ulcers appeared improved by x-ray at the end of this time.

Symptoms the same. X-rays unimproved or worse. 14 cases, 58.3%.

These cases did not heal after the administration of the injections, even though a dietary regime of an average of 2.8 years had been subsequently maintained.

CONCLUSION

Peptic ulcer tendency is inherited, and is in some way associated with the hyposthenic body type, and a derangement of the autonomic system, with a tendency towards vagotonia.

These tendencies make it possible for an ulcer to appear when the proper environmental factors present themselves. These factors might be in themselves important directly or through their effect on the sympathetic system which is already under par.

These factors are:

1. Climatic changes

a. Cold weather predisposes to respiratory infections

b. Warm weather causes:

- (1) A decrease in the gastric acidity
- (2) Increase in vitamin intake
- (3) Increase in ultra-violet and infra-red rays

2. Dietary Indiscretions

3. Factors which make for unrest and nervous strain

Ulcers occur in men in the third decade when they are under the greatest strain in their daily life.

The association between the etiology of peptic ulcer and increased hydrochloric acid content of the stomach is shown. In patients whose ulcers healed the hydrochloric acid content of the stomach decreased. It decreased also in patients whose ulcers became dormant, or non-active. It remained the same or became greater in patients whose ulcers remained active.

Facts are given showing that increased acidity is not the cause of pain, nor is necessarily increased tone or peristalsis of the stomach, unless the ulcer is attached to the muscle coat proper.

It must be stressed that peptic ulcers, especially gastric ulcers, heal by medical treatment. Also that once an ulcer has healed it usually remains healed. Recurrent ulcers are usually the same ulcers which have become activated after a resting period.

The healing of a peptic ulcer is accomplished in only a few months when the ulcer is a recent and superficial one. When an ulcer is calloused its healing may be a question of several years. However, the patient will not have any gastro-intestinal symptoms during this time if he maintains his diet; nor is his diet very drastic. The dietary regime consists of a liquid diet in the beginning. Usually 8 ounces of milk, warmed to body temperature, are given every hour from 8 A. M. to 8 P. M., until the pain is controlled, that is, in about two to three days. In the beginning, also, phenobarbital is given to quiet the nerves, a non-spasmodic to relieve the spasm of the stomach and the duodenum, and other substances to reduce the gastric acidity, be it bismuth, aluminum hydroxide or silicate, and finally a substance such as heavy magnesium oxide or milk of magnesia to act as a cathartic.

After a few days the strained liquid from vegetable soups may be given, as well as fruit juices and milk combinations. These are given in quantities of 8 ounces every hour for twelve hours, and continued for about two weeks, after which a soft solid diet is allowed. Finally, after a month or two, the patient is given broiled lamb or steak. Of course no condiments, alcohol, or tobacco should be used.

Since the majority of our patients must work, the treatment outlined above is most often used. However, whenever it is possible, we like to hospitalize our patients for four to eight weeks, during which time they are fed through a duodenal tube. Under this management the pain and other gastro-intestinal symptoms are more quickly relieved. The liquids are fed every hour through the duodenal tube, which prevents the foods from coming in contact with the ulcer-bearing area. Sometimes the ulcer will disappear during the course of intubation. If the ulcer is still present after this treatment, the patient is placed on a soft solid diet and anti-peptic ulcer medications and kept on this routine until the ulcer disappears. When it is considered that this diet is one in name only, no hardship is really felt.

There is no short-cut in the healing of ulcers. The diet is the principal treatment. It is wise to remove all factors which reflexly affect the gastro-intestinal tract, whether they be nervous, chemical or infectious. The finding of a situation which will bring the patient more into the fresh air, sunlight, and warmth, will hurry the cure. Even the giving of ultra-violet light at home is of benefit. Other factors which build up body resistance, such as rest, plenty of sleep, and vitamins, not only prevent infections, especially of the upper respiratory tract which require aspirin (a very strong stomach irritant) but are in themselves important in healing.

There are no injection treatments of any value specifically for the ulcer. In the majority of cases, surgery should not be resorted to in hemorrhage. Surgery is necessary in the treatment of perforations. Again, unless the inflammatory edges of the ulcer are removed, the ulcer is merely reconstructed, and the ulcer and its symptoms return. Surgery is needed in those forms of obstruction which are the result of scar tissue.

The majority of obstructed cases are due to a reflex spastic condition of the pylorus, and these should be treated medically. Surgery must always be combined with good medical post-operative care, or the results will be worse than if no operation had been performed, for we may have the ulcer, as well as the surgical procedures to contend with.

In the hands of the majority doing surgery, the posterior gastro-enterostomy is the best type of surgery to do. Surgery effects its cures in some cases by the neutralization of the gastric content, in others by allowing the ulcer to rest, through short circuiting, and in others by the relief of obstruction.

Gastric ulcers will heal in 4 to 5 weeks, and duodenal ulcers in 2 to 3 months after this operation. The number of gastro-jejunal ulcers occurring after this depends in some cases upon how thorough an alkalization is

obtained and upon how long and well the stoma was made.

Subtotal gastric resection is being popularized now on the theory that few gastro-jejunal ulcers occur after

this operation, possibly because of greater alkalization. This may be so, but the number of patients that will die from the operation may more than account for the difference.

REFERENCES

- Allen, N. M., quoted by F. H. Lahey: Gastro-jejunal Ulcer and Gastro-jejunocolic Fistula. *Surg., Gyn., Obst.*, 61:599-612, (Nov.) 1935.
- Bergsma, S.: Gastric and Duodenal Ulcer in the Black People of Abyssinia. *Arch. Int. Med.*, 47:144, (Jan.) 1931.
- Cocci, quoted by Evelina Liberatori: Roentgenologic Observations on the Resected Stomach Following Surgical Intervention. *Am. J. Roent.*, 38:268, No. 2, (Aug.) 1937.
- Einhorn, M.: Seasonal Incidence and Study of Factors Influencing the Production of 1,000 Recurrences of Gastroduodenal Ulcers in 800 Patients. *Am. J. Med. Sc.*, 179:259, (Feb.) 1930.
- Fowler, W. and Hurewitz, H. M.: Bleeding Peptic Ulcer. *J. of Iowa State Med. Soc.*, 25:115, (March) 1935.
- Graves, A. M.: Perforated Peptic Ulcer. *Internat. S. Dig.*, 16:259-267, 1933.
- Hingston, B. H.: Some Observations on Gastric and Duodenal Ulcers in Bengal. *Indian Med. Gazette*, 62:543, (October) 1927.
- Hinton, J. W.: Massive Hemorrhage. *Ann. Surg.*, 101:56, (March) 1935.
- Lahey, F. H. and Swinton, N. W.: Gastro-jejunal Ulcer and Gastro-jejunocolic Fistula. *Surg., Gyn., Obst.*, 61:599-612, (Nov.) 1935.
- Lewisohn, R.: Late Results in Perforated Gastro-duodenal Ulcers. *Ann. Surg.*, 87:855-860, 1928.
- Muller, H.: Geographic Distribution of Peptic Ulcer. *Am. J. Surg.*, 23:497, (March) 1934.
- Sturtevant, M. and Shipiro, L. L.: Gastric and Duodenal Ulcer. *Arch. Int. Med.*, 38:41-56, 1926.

Editorial

PROCTOLOGY AND GASTROENTEROLOGY

IT HAS LONG been the author's contention that there is an intimate and necessary relationship between proctology and gastroenterology. The arbitrary division of the intestinal tract at the level of the ileo-caecal junction, or at the upper sigmoid, with the upper intestinal tract delegated to the gastroenterologist and the lower segment relegated to the proctologist is an unfortunate and undesirable interruption of continuity. It is unfortunate both for the patient and for the physician. Specialization is desirable, but when the range of vision is too greatly narrowed much of importance is missed, both therapeutically and diagnostically.

Some proctologists limit themselves entirely to the rectum and anus. This is comparable to specializing in the removal of cataracts from the left eye only. Others limit their field to the anus, rectum and sigmoid, and do no surgery in any of these regions. These are injection proctologists. The great danger in this event is the tendency to treat all cases by injection, regardless of criteria or indication. Then there are the proctologists who extend their surgical domain to the ileo-caecal junction, and include the appendix as well. These specialists usually meet with active opposition at the hands of the general surgeon.

It is at this point that the gastroenterologist often enters the field of dispute. From a medical viewpoint the colon is claimed by this specialist. Indeed, the gastroenterologist often includes the injection therapy of hemorrhoids in his specialty. This is subject to the same dangers above noted, with a disregard of proper criteria for this form of therapy. A further point of conflict arises in the question of roentgenography of the colon. Should this examination be in the hands of the roentgenologist, the gastroenterologist or the proctologist? Of course it should be in the hands of any one of the three, if he is competent to perform the examination and interpret the results. If the complaint seems refer-

able to the colon it is the opinion of the author that the proctologist should perform the roentgen study. It is true, however, that many apparent colon complaints are actually of gastric origin. The significance of this fact is that the competent proctologist must either work in close cooperation with the gastroenterologist, or must himself be trained to examine the upper gastrointestinal tract as well.

The close relationship between the various endoscopic procedures leads to the thought that a trained endoscopist such as the proctologist might do well to further adapt his skill to gastroscopy. Gastroscopy, with the flexible gastroscope, is a relatively simple and safe procedure. In some hospitals gastroscopy is the function of the otolaryngologist. Why that should be the case is beyond the understanding of the author. The gastroenterologist thinks nothing of including sigmoidoscopy in his diagnostic armamentarium, and indeed he should. Certainly, then, the gastroenterologist can have no objection to a careful intestinal study by the proctologist, including gastroscopy. Schindler includes, among his indications for gastroscopy (2), "bowel distress, unexplained gastro-intestinal hemorrhage, sprue, enteritis and colitis." This is true because changes in the gastric mucosa frequently occur in cases of colon pathology, and further because symptoms apparently referable to the colon may actually be of gastric origin.

A careful general examination should precede all proctologic investigations (1). This is true of every case. Hemorrhoids may represent hepatic cirrhosis. The passage of blood by rectum may indicate a blood dyscrasia among other (and numerous) possibilities. A complete general and gastro-intestinal study is indicated in such cases.

In a personal communication from a noted gastroenterologist, associated with this country's outstanding clinic, the observation is made that he is often called upon to examine patients whose ultimate diagnosis may be scoliosis, although the symptoms may be apparently gastro-intestinal in nature. The importance of general

examination in every problem, gastro-intestinal and proctologic, cannot be over-emphasized.

The significance of these statements is not that the separate specialties of gastroenterology and proctology cannot exist, but that they must of necessity overlap. This results in a need for close cooperation between the proctologist and the gastroenterologist in many cases. Better still would be the inclusion of gastroenterologic training in the armamentarium of the proctologist. Indeed the combination of gastroenterology

and proctology as a specialty is much more logical than the customary and accepted combination of eye, ear, nose and throat under one heading. This new specialty might be designated as gastroenteroproctology or proctenterology.

In summary we may conclude that either the gastroenterologist and the proctologist must cooperate closely in the study of many problems, or they must each seek additional training. The ideal combination would be found in the specialist who is trained in both fields.

REFERENCES

1. Cantor, Alfred J.: Ambulatory Proctology. Paul B. Hoeber, Inc., New York, 1946.

2. Schindler, Rudolf: Gastroscopy the Endoscopic Study of Gastric Pathology. The University of Chicago Press, Chicago, 1937, p. 82.
— Alfred J. Cantor, M.D.

Book Review

Diabetes. By Henry J. John, M.A., M.D., F.A.C.P., pp. 300, St. Louis, Mo., C. V. Mosby Company, 1946.

This is a book one becomes fond of, simply because the author has concentrated on only two points, the diagnosis and the treatment of diabetes mellitus. He has omitted a great deal of "padding" which tends to clutter up many otherwise excellent texts; he is not dependent on tradition but reports what he himself has learned about this disease. Hyperglycemia, from any cause, if continued, produces diabetes through a degen-

erative effect on the pancreas. The diagnosis of diabetes is made by finding an abnormal elevation of the post-prandial blood sugar. The effectiveness of treatment can only be gauged by following the post-prandial blood sugar levels. The book stresses the importance of "pancreatic rest" through insulin treatment in cases of hyperinsulinism. The section on childhood diabetes is especially valuable. The book is recommended to all students of the disease who desire a concise and practical monograph.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
*J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

* With the Armed Forces.

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

CLINICAL MEDICINE

LARSON, E. A. AND EVANS, G. T.: *Biliverdin icterus.* (Proc. Central Soc. Clin. Res., v. 17, p. 31, 1944).

A direct colorimetric method for the determination of serum biliverdin is described; it employs the Evelyn colorimeter and depends for its validity on the increasing light absorption of biliverdin in passing from green to red wave lengths, as compared with the decreasing or unchanging absorption of bilirubin, reduced

hemoglobin, and oxyhemoglobin in passing through the same range. Methemoglobin must be specifically excluded. Normal sera contain no detectable biliverdin (less than 0.05 mg.%). 93 observations were made on the sera of 63 consecutive cases of jaundice. The biliverdin values ranged from 0-2.2 mg.%. When biliverdin is present, the general trend is for the higher values to occur in cases with the higher values for total bilirubin; thus, the 6 highest values for biliverdin (over 1 mg.%) were in cases (3 carcinomatous obstruction, 2 common duct stone, 1 catarrhal jaundice) having to-

tal bilirubin above 17 mg.% (average 24.4 mg.%). A significant level of biliverdin was found in every case of the following: carcinomatous obstruction of the common bile duct (26 cases); catarrhal jaundice (4 cases); cirrhosis with jaundice (5 cases); and common bile duct stricture (5 cases). Among the above cases in which biliverdin was uniformly present there were 14 cases with total bilirubin under 10 mg.% (average 5.9 mg.%); compared with this it is worthy of note that of the 10 cases of common bile duct stone, 5 cases with an average total bilirubin of 7.1 mg.% had no biliverdin in their sera. The remaining 13 cases (6 transfusion reactions, 3 hemolytic anemia, 1 leukemia, 1 Hodgkin's disease, 1 Banti's syndrome, 1 cardiac decompensation) with average total bilirubin of 7.6 mg.% (range 3-30 mg.%) all had zero biliverdin. The green tint of the patient was noted in cases having as little as 0.3 mg.% biliverdin (total bilirubin 9-20 mg.%). Serial observations in 14 patients showed that biliverdin can change markedly in 1-5 days without respect to the direction of change of the total jaundice. In 3 of these cases, during a period when there was a notable high caloric intake, the biliverdin was observed to disappear despite absence of marked change in the total jaundice. In general it may be said that biliverdinemia is a further evidence of regurgitation jaundice, and has not been observed in hemolytic (retention) jaundice. The absence of biliverdinemia speaks against the diagnosis of jaundice due to cancer. — Courtesy of Biological Abstracts.

HOAGLAND, C. S.: *Suggestions for therapy of acute infectious hepatitis*. (*Bull. N. Y. Aca. Med.*, v. 21, p. 537, Oct. 1945).

Among military personnel infectious hepatitis (epidemic jaundice) became one of the major medical problems. Morbidity was high and convalescence long. In civilian populations it has also been a common disease, one that has often been termed catarrhal jaundice. The maximum damage to the liver occurs early in the disease. Most of the illness actually occurs during the period when the liver has already sustained the maximum damage and is in the process of reparative regeneration. Repair should be encouraged by proper diet and bed rest. High protein-high carbohydrate diet is essential but whether the fat content should be kept low is still unknown. Parenteral amino acids may be given with beneficial results. The value of methionine in therapy is questionable. Both oral and parenteral administration of fat-soluble vitamins A, D, and K may be necessary since their metabolism by the liver may have been interrupted. — M. H. F. Friedman.

BRENT, M. J., TURNER, E. L., HALLOWAY, G. D. AND CUFF, J. R.: *Value of brewer's yeast in preventing icterus in pneumonia*. (*Southern Med. J.*, v. 38, p. 730, 1945).

Nine dogs were fed a diet of fat meat, overcooked turnip greens, corn meal and sorghum. (This diet was said to be representative of that used by many Negro families in the southern states.) The dogs were then

subjected to pneumonia induced experimentally. All the animals developed positive van den Bergh reactions. Fatty liver degeneration was found at autopsy. In a second series of eleven dogs, similarly restricted to the above diet and subjected to pneumonia, brewers' yeast was included. After the pneumonia was induced only one animal showed liver injury and none showed positive van den Bergh reactions. The authors state that these results on dogs confirm the conclusions drawn from a study of the etiology of icterus in pneumonia among Negroes. They found that Negro patients with pneumonia did not develop an icterus if vitamin B complex were administered. — M. H. F. Friedman.

HUGHES, J. O.: *Treatment of infectious hepatitis by diet and rest*. (*U. S. Army Med. Bull.*, v. 5, p. 662, Dec. 1945).

Complete bed rest and a diet high in both protein and carbohydrate but low in fat were found to produce gratifying results in 26 cases of acute infectious hepatitis. As compared with 19 other cases, who were permitted freedom as to activities and food, the bed-rest group required shorter hospitalization and showed evidences of more prompt improvement. The liver size returned to normal sooner and both the cephalin-cholesterol flocculation test and icterus index pointed to a more rapid resumption of normal liver functions. The study does not reveal whether the bed rest or the special diet is the more important of the two factors in producing the benefits noted. — F. X. Chockley.

HARGREAVES, W. H.: *Chronic amebic dysentery: new approach to treatment*. (*Lancet*, p. 68, July 21, 1945).

Hargreaves reports on 47 cases of amebic dysentery that resisted standard courses of treatment. The history of one patient is outlined in detail to illustrate the newer approach. The patient had been hospitalized in India and England for more than a year with no evidence of improvement. He complained of abdominal pains, was cachectic, feverish, and had up to twenty foul stools a day. Blood and ameba were present in the stools. Emetine was ineffective. Following an initial intra-muscular dose of 100,000 units of penicillin and 33,000 units every three hours (to a total of 1,000,000 units) the patient showed dramatic improvement and on the day following termination of treatment he was free of both pain and fever. On the second day he passed the first formed stool in two years. Although he regained his weight he experienced a relapse after two weeks and required a second course of treatment with 2,250,000 units of penicillin. Improvement was again noted and sigmoidoscopic examination now showed a healthy colon. The author gives in addition to penicillin a course of succinylsulfathiazole by mouth to reduce the organisms which are resistant to penicillin. In addition to chronic amebiasis he has treated successfully in a similar manner a number of cases of chronic ulcerative colitis. — F. E. St. George.

MUELLER, R. S.: *Local use of sulfanilamide in the treatment of acute appendicitis.* (*Ann. Surg.*, v. 122, Oct. 1945).

This paper reports the benefits obtained during the period 1940-44 from sulfonamide preparations used locally in 320 out of 739 cases of acute appendicitis. Contrasted with 742 cases surgically managed during 1935-39 without the use of sulfonamides, the reduction in mortality was great — 0.4 per cent as against 2.83 per cent. Local use was preferred because of the higher concentration of the drug thus made possible at the site of infection. Peritoneal drainage should not be abandoned. When abscess or peritonitis due to rupture is found the author advocates penicillin in addition to local sulfonamide application because in these cases some of the organisms may be sulfa-resistant. — N. M. Small.

BOWEL

LECIAN, E.: *Influence of Tuberculin on Intestinal Ulcers.* (*Lékarští Listy*, v. 1, No. 7, pp. 146-150, 1946).

62 cases of gastric or duodenal ulcer were treated with old tuberculin, using increasing doses from 0.1 mgm. to 1.0 mgm. In 95 per cent of the patients favorable results were observed. Author believes that the healing effect of tuberculin is due to the hyperemia of the gastric mucosa caused by these injections. Attention is called to the dangers of this treatment. Tuberculin is recommended only when other methods failed. — O. Felsenfeld.

VESELY, B.: *Lymphoblastoma of Peyer's plaques clinically resembling typhoid fever.* (*Casopis Lékarů Ceskych*, v. 85, No. 11, pp. 384-385, 1946).

A case showing the clinical picture of typhoid fever but with negative serology is described. The patient died of a perforation of the ileum. Histologic examination revealed a lymphoblastoma of the patches of Peyer. — O. Felsenfeld.

HORA, F.: *Septic typhoid fever.* (*Casopis Lékarů Ceskych*, v. 85, No. 4, pp. 122-123, 1946).

During the recent epidemic of typhoid fever in Moravia, many cases of septic typhoid fever were observed. The temperature resembled that of malaria. The spleen was greatly enlarged. The blood picture showed leukocytosis with a shift to the left. While intestinal bleeding was not observed, myocarditis occurred often. — O. Felsenfeld.

STOMACH

KRONDL, A.: *Difficulties encountered in the diagnosis of atrophic gastritis.* (*Casopis Lékarů Ceskych*, v. 85, No. 6, pp. 188-191, 1946).

36 cases of atrophic gastritis were studied and classified as diffuse, focal or mixed types. While X-ray examination was not reliable in all cases, gastroscopy permitted to secure the diagnosis in every patient. No connection was found between anatomic picture, se-

cretion of gastric juice and blood findings. — O. Felsenfeld.

EXPERIMENTAL MEDICINE

PATHOLOGY

ANDERSEN, T. T. AND TULINIUS, S.: *Experimental chronic hepatitis (cirrhosis) based on infection.* (*Acta Med. Scand.*, v. 104, p. 550, 1940).

A brief review is given of some of the literature pertaining to the attempted induction of cirrhosis in experimental animals, and some original experiments with pigs are described. The technique was apparently that adopted in earlier studies but in view of the topical importance of the subject, the experimental data are abstracted in some detail. Duodenal juice was extracted, by means of an Einhorn duodenal tube, from human patients with epidemic hepatitis, and 25 ml./head was fed by mouth (mixed with the food) to 2 piglets 6-8 weeks old which for 10 days prior to the experiment had received a quantitatively poor but qualitatively adequate diet, of which no details are given. It is stated that the disease does not occur in the case of normally fed animals. Minced liver from pigs in which disease had been set up with human duodenal juice was then fed to 2 other piglets, and in 2 more cases, liver from jaundiced pigs obtained from an abattoir was fed. No clinical or pathological details of the naturally jaundiced pigs are given. One of each pair of pigs was slaughtered on the 4th day, by which time the blood plasma in both cases was slightly icteric and the liver was enlarged, swollen, soft, pale, and brownish-yellow in color, with an indistinct pattern and with microscopic evidence of acute parenchymatous damage, the hepatic cells showing granular cytoplasm and pyknotic nuclei, and the vessels being compressed. The other member of each pair was fattened for 10 months, by which time the weight was 200 kilograms. On slaughter, the liver of both animals was enlarged, dark, granular, and extremely firm, with some degree of perihepatitis. There was histological evidence of inflammation, mainly intestinal, regarded as pre-cirrhotic. The livers of negative controls remained normal. — Courtesy of Biological Abstracts.

PATHOLOGICAL CHEMISTRY

CUTHBERTSON, E. M. AND GREENBERG, D. M.: *Chemical and pathological changes in dietary chloride deficiency in the rat.* (*J. Biol. Chem.*, v. 160, p. 83, 1945).

Rats were kept on a diet greatly deficient in chloride, namely at an intake of less than 2 to 5 milligrams per cent weight of food. The growth was severely affected. The kidney damage was also severe and in the later stages involved the whole nephron. The heart and spleen were the only tissues which did not show reduction in the chloride content. There was evidence that a state of alkalosis had developed since the urinary excretion of citrate was increased by about twenty times. — G. Klenner.

SEHRA, K. B. AND AHMAD, B.: *Studies on Ca and P metabolism. III. Hepatic inefficiency and rickets.* (*Indian Jour. Med. Res.*, v. 33, p. 115, 1945).

In order to study the relationship between liver function, blood serum phosphatase and bone development, the degree of bone calcification in guinea pigs which were fed carbon tetrachloride to produce liver damage has been examined. It was observed that the degree of calcification was lower in animals with liver damage than that of normal controls. The addition of oats to the diet of these animals further aggravated the decalcifying action resulting from liver damage. The role of phosphatase in the mineral metabolism of the skeleton is discussed. — Courtesy of Biological Abstracts.

METABOLISM AND NUTRITION

STRUMIA, M. M., BLAKE, A. D., RAIDER, H. C., AND CHORNOCK, F. W.: *The use of a "modified globin" from human erythrocytes in hypoproteinemias.* (*Am. J. Med. Sc.*, v. 211, p. 51, Jan. 1946).

The authors use the globin fraction of hemoglobin derived from discarded red blood cells to correct hypoproteinemias of diverse origin. They present evidence that modified human globin may be advantageously used in many patients, especially those who cannot be adequately fed by mouth or who have impaired liver and/or kidney function; and those who present themselves with severe hypoproteinemia and must be prepared for operation within a very short period of time.

Plasma may be physiologically and pharmacologically the ideal material for intravenous nitrogenous feeding, but great quantities are needed for severe hypoproteinemic patients. With the use of modified globin four times as much protein can be made available from the same quantity of blood.

In the human a definite increase in the circulating plasma protein and hemoglobin occurs and the utilization of globin for plasma protein production is about 3:1. There is also an increase in urinary output, increase in volume of circulating blood, a change from a negative to positive nitrogen balance and a general improvement in the clinical course as shown by amelioration of anemia and reduction of edema. In addition, where intravenous amino acids fail to cause an adequate response, such as in severe hypoproteinemia, marked reduction in plasma protein reserves, or liver and kidney damage, modified globin can be used intravenously with good results. — C. De Barardinis.

MISCELLANEOUS

HILOUCAL, L., SMEJKALOVA, J. AND CRCKA, Z.: *Electrocardiographic changes in typhoid fever.* (*Casopis Lékarů Ceskyh*, v. 85, No. 10, pp. 333-339, 1946).

The EKG of 100 patients with typhoid fever was studied. 63 of them showed changes, mainly during the 3rd and 4th week of the disease. Most alterations concerned the "T" wave. Authors believe that these changes are more of functional than of organic nature. — O. Felsenfeld.

HASIB TANYOL: *A new method of diagnostic splenic puncture.* (*Türk Tıp Cemiyeti Mecmuası*, v. 11, No. 12, pp. 525-533, 1946).

The colon is insufflated before the operation. The puncture is carried out only when at least the inferior pole of the spleen is accessible to palpation. Two assistants are used. The patient lays on his back. One of the assistants, standing on the left side of the patient, puts his hands over the ribs and compresses the abdominal wall with his fingers until the spleen is felt. The second assistant, standing on the right of the patient, presses the abdominal wall about four-five inches below the spleen. The needle is introduced in the depression created by the pressure, pointing upward. No rupture was observed when this method was used. — O. Felsenfeld.

SCHROTT, J.: *Spleen tumor in typhoid fever.* (*Lé-karské Listy*, v. 1, No. 2-3, pp. 42-45, 1946).

The spleen tumor in typhoid fever represents an allergic-granulomatous reaction of the reticuloendothelial system. Splenomegaly after typhoid fever may be the result of suppuration. A case of such a splenic abscess cured by aspirations is described. — O. Felsenfeld.

MATOUSKOVA-KRAVKOVA, L.: *On the therapy of typhoid fever with bacteriophage.* (*Lé-karské Listy*, v. 1, No. 2-3, pp. 36-38, 1946).

92 patients were treated. The epidemic was severe. Complications, as intestinal perforations and extra-intestinal suppurations, were frequent. Phage therapy did not influence temperature, diarrhea, complications or mortality. — O. Felsenfeld.

Differences in Excretion of Hippuric Acid and Glucuronates After Ingestion of Sodium Benzoate and Benzoic Acid

By

I. SNAPPER, M.D., E. GREENSPAN, M.D.

and

A. SALTZMAN, M.D.*

NEW YORK, N. Y.

IT HAS BEEN KNOWN for many decades that after ingestion of sodium benzoate the urine reduces copper and bismuth solutions (1). This proves that the administration of sodium benzoate leads not only to the excretion of hippuric acid but also to the formation of another conjugation product of benzoic acid. In 1907 Magnus Levy (2) demonstrated that the reducing power of the urine is due to the excretion of a compound consisting of benzoic acid and glucuronic acid. He isolated this substance from the urine of a sheep in the form of a strychnine salt. In 1924 J. Neuberg (3) from Amsterdam determined separately the total conjugated benzoic acid in the urine and the benzoic acid present in the form of hippuric acid. In this way, he showed that in normal individuals 7 to 12% of the benzoic acid ingested was excreted as a benzoyl glucuronic acid compound. Quick (4) in 1926 crystallized this compound in pure form and studied its metabolism in great detail (5), using a modification of the method of Neuberg. For several years chemists differed in opinion about the structural formula of this substance (6), but it is now generally accepted that this compound should be designated as benzoyl glucuronate (7).

In the following paragraphs it will be explained that the amount of benzoyl glucuronate excreted differs considerably depending on whether benzoic acid or sodium benzoate is ingested.

METHODS

Normal volunteers took 5.8 grams of sodium benzoate and two days later the equivalent dose of 5 grams of benzoic acid. These quantities were divided in about ten small doses, each of which was wrapped in a moistened powder wafer (Alpinol Corp.). The wafers were swallowed with water and the total quantity was ingested within ten minutes. After the ingestion of each wafer a piece of bread was eaten. These wafers mask the taste of the benzoic acid and its salts completely, and as they are made of dough, are immediately dissolved in the stomach. Immediately after the ingestion of the wafers, a breakfast of bread and coffee with milk was given.

Three 2-hour specimens of urine were collected and examined.

For other experiments 5.8 grams of sodium benzoate were dissolved in 180 cc. of water. Normal volunteers

took 20 cc. of this solution every 30 minutes in the course of four hours. Urine was collected every two hours after the start of the experiment.

1. Hippuric Acid Determination.

The urine is acidified with acetic acid and evaporated before a fan on a sandbath at 40° C until a volume of about 10 to 20 cc. is left. 2 cc. of strong HCl are added and the mixture is left overnight in the icebox. The crystalline mass is filtered under suction, washed with 50 cc. of ice cold water and dried in the exsiccator. Hippuric acid is determined by weighing. The weight is corrected with the hippuric acid contained in the filtrate and washwater (300 mgm. hippuric acid per 100 cc.).

2. The total reduction of the urine is determined by the Shaffer-Hartmann method. The quantity of glucuronic acid is obtained by adding 7.7% to the glucose value.

3. Qualitative glucuronic acid reaction. 0.1% of the total volume of urine excreted is used for the test. When the total volume of a 2-hour fraction is 100 cc. then 0.1 cc. are taken; when the total volume is 200 cc. 0.2 cc. are taken, etc. This quantity is diluted with water to 2 cc. Then 2 cc. of strong HCl and 2 cc. of 0.2% filtered watery naphthoresorcinol solution are added. The naphthoresorcinol solution is renewed every week. The mixture is heated in a boiling water bath for exactly 10 minutes, then cooled on ice, and the blue pigment formed shaken out with 2 cc. of amyl alcohol (8).

TABLE I illustrates the following points:

1. There is usually no difference between the total quantity of hippuric acid excreted within 6 hours after ingestion of 5.8 grams of sodium benzoate or after ingestion of 5 grams of benzoic acid.

2. Each individual excretes during the first two hours after the ingestion of 5.8 grams of sodium benzoate more hippuric acid than in the first 2-hour fraction after ingestion of 5 grams of benzoic acid.

3. The third 2-hour fraction usually contains an appreciable amount of hippuric acid after ingestion of 5 grams of benzoic acid, much less after administration of sodium benzoate.

4. After ingestion of 5.8 grams of sodium benzoate the glucuronic acid reactions are without exception strongly positive in the first 2-hour fraction. In most cases the second 2-hour fraction also shows an appreciable

*From the Second Medical Service, Mount Sinai Hospital, New York.
Submitted January 18, 1946.

ciable glucuronic acid reaction. In the third 2-hour fraction, the reaction is always negative. After ingestion of 5 grams of benzoic acid the glucuronic acid excretion has always been negative in the first and third 2-hour fractions; occasionally a doubtful reaction has been found in the second 2-hour fraction.

5. The total reduction of the urine is usually (one exception) stronger after ingestion of 5.8 grams of sodium benzoate than after ingestion of 5 grams of benzoic acid.

These figures seem to indicate that in normal persons,

(a) the excretion of hippuric acid is more rapid after ingestion of sodium benzoate than after ingestion of an equivalent quantity of benzoic acid,

(b) the excretion of benzoyl glucuronate is consider-

with glycine is then conjugated with glucuronic acid. The absorption of benzoic acid from the intestinal tract is less rapid. At no time is the liver overwhelmed with benzoic acid and the glycine conjugation in the liver suffices for the detoxication of the benzoic acid. There is no occasion for the formation of benzoyl glucuronate.

However, other explanations cannot be excluded. A temporary acidosis, which could well result from the ingestion of 5 grams of benzoic acid, might influence the conjugating power of the liver or even the availability of glycine and in this way depress the formation of hippuric acid.

It is true that Quick (9) has not been able to influence the formation of glucuronates in dogs after ingestion of sodium benzoate either by ingestion of sod-

TABLE I

Excretion of Glucuronic Acid and Hippuric Acid after Rapid Ingestion of 5.8 Grams of Sodium Benzoate and 5 Grams of Benzoic Acid

		Urine volume in ml.			Naphthoresorcinol reaction			Glucuronic acid reduction in milligrams			Hippuric acid excretion in grams		
		I ¹	II ²	III ³	I ¹	II ²	III ³	I ¹	II ²	III ³	I ¹	II ²	III ³
Sn.	Na ⁴	365	520	120	+++	—	—	330	234	114	3.6	3.12	traces
	Ac ⁵	1025	450	128	—	±	—	280	125	119	1.62	3.30	1.43
La.	Na ⁴	200	115	97	+++	+	—	390	190	175	4.00	2.30	0.180
	Ac ⁵	190	280	130	—	±	—	143	254	93	1.88	4.30	0.360
Rob.	Na ⁴	180	150	312	+++	+±	—	230	173	81	3.62	2.42	0.130
	Ac ⁵	791	295	355	—	—	—	221	225	95	2.60	2.45	0.820
Gr.	Na ⁴	275	168	167	++	++±	—	431	294	168	4.70	2.24	0.080
	Ac ⁵	845	525	190	+	—	—	187	170	143	1.28	3.07	0.725
Ros.	Na ⁴	184	130	244	++±	++	—	288	166	115	4.46	2.37	0.710
	Ac ⁵	380	108	66	—	—	—	184	123	119	2.51	2.53	0.020
Ha.	Na ⁴	134	120	60	++	+	±	256	244	131	2.81	2.96	0.040
	Ac ⁵	156	94	98	—	—	—	180	105	?	2.50	1.90	1.33
Sa.	Na ⁴	108	111	75	++	±	—	286	215	256	3.685	3.31	0.350
	Ac ⁵	85	205	110	—	—	—	194	299	219	2.10	4.36	0.685
Ge.	Na ⁴	167	86	100	+++	+	—	280	131	204	3.66	2.52	0.48
	Ac ⁵	150	118	90	—	+	—	x	x	x	1.89	4.03	0.805
Tu.	Na ⁴	180	108	52	+±	++	—	258	x	x	3.32	3.45	0.560
	Ac ⁵	198	118	124	—	—	—	264	169	220	2.45	3.00	1.51

¹ 1st 2-hour specimen

² 2nd 2-hour specimen

³ 3rd 2-hour specimen

⁴ 5.8 grams of sodium benzoate taken in powder wafers within 10 minutes

⁵ 5 grams of benzoic acid taken in powder wafers within 10 minutes

* Ate a pear for luncheon

able only after ingestion of sodium benzoate and is negligible after ingestion of benzoic acid.

From these results it must be concluded that the detoxication of benzoic acid is different depending on whether the substance is ingested as a sodium salt or as the acid itself.

It is obvious that the difference in conjugation may well be connected with a difference in the rapidity of absorption. The excretion of hippuric acid as shown in TABLE I seems to indicate that the soluble sodium salt of benzoic acid is absorbed more readily than the only slightly water soluble benzoic acid. It might be reasoned that the glycine conjugation in the liver is not rapid enough to take care of the large amounts of sodium benzoate absorbed within the first two hours from the intestinal tract. The benzoate which cannot be combined

ium bicarbonate or of ammonium chloride. On the other hand, Quick's interesting experiments seem to indicate that under some special circumstances acidity in the widest sense of the word may have an unfavorable influence upon the formation of glucuronates. Substitution in the ortho-position of benzoic acid with an acidic group (nitro-, halogen, or hydroxy) caused a decrease in the glucuronate excretion whereas substitution with an alkaline group (amino) produced an increase of the glucuronate excretion. It should be stressed that this rule holds only for ortho-substitution products because substitution in the meta-position with acid groups increases the output of glucuronates. Finally, Quick concluded that a close relationship exists between the ionization constant of the substituted derivatives of benzoic acid and the rate with which these

compounds are excreted combined with glucuronic acid (10).

These results of Quick made it necessary to investigate whether the slow absorption of benzoic acid or the acidic character of this substance is the reason for the low rate of glucuronate formation after the intake of benzoic acid compared with the liberal amounts of glucuronate excreted after ingestion of sodium benzoate.

For this purpose 5.8 grams of sodium benzoate were administered divided in nine equal doses. Each of these doses were taken at intervals of 30 minutes over a period of four hours.

now shows the presence of considerable amount of hippuric acid. It follows that the pattern of hippuric acid excretion, after slow ingestion of 5.8 grams of sodium benzoate over a 4-hour period, is comparable with that observed after ingestion of a single dose of 5 grams of benzoic acid. The latter result is shown in TABLE III where the averages of excretion of hippuric acid, of benzoyl glucuronate and of reduction values expressed as glucuronic acid are compiled.

As shown in TABLE II the delay in absorption of sodium benzoate when 5.8 grams are administered in nine doses over a 4-hour period results in negative glu-

TABLE II
Excretion of Glucuronic Acid and Hippuric Acid after Rapid and after Slow Ingestion of 5.8 Grams of Sodium Benzoate

	Intake of 5.8 grams of sodium benzoate	Volume in ml.				Naphthoresorcinol reaction				Glucuronic acid in milligrams determined by reduction				Hippuric acid in grams			
		I ¹	II ²	III ³	IV ⁴	I ¹	II ²	III ³	IV ⁴	I ¹	II ²	III ³	IV ⁴	I ¹	II ²	III ³	IV ⁴
Sn.	Rapid ⁵	365	520	120		+++	—	—	—	330	234	114		3.6	3.12	Traces	
	Slow ⁶	95	128	79	77	—	—	—	—	205	193	170	207	2.28	3.45	1.377	0.370
L.	Rapid ⁵	200	115	97		+++	+	—	—	390	190	175		4.00	2.30	0.180	
	Slow ⁶	74	76	350	156	—	—	—	—	160	165	236	186	1.93	2.85	1.90	0.364
Rob.	Rapid ⁵	180	150	312		+++	±	—	—	230	173	81		3.62	2.42	0.130	
	Slow ⁶	132	475	596	145	—	—	—	—	143	180	257	132	2.1	3.0	0.91	0.207
Gr.	Rapid ⁵	275	168	167		++	++±	—	—	431	294	168		4.70	2.24	0.080	
	Slow ⁶	84	82	50	75	—	—	—	—	201	143	138	196	2.82	2.70	1.42	0.140
Ros.	Rapid ⁵	184	130	244		++±	++	—	—	288	166	115		4.46	2.37	0.710	
	Slow ⁶	138	144	106	44	—	—	—	—	241	202	241	114	2.61	3.62	1.68	0.090
Ha.	Rapid ⁵	134	120	60		++	+	±	—	256	244	131		2.81	2.96	0.040	
	Slow ⁶	176	114	87	39	—	—	—	—	234	222	229		2.75	2.86	1.14	
Sa.	Rapid ⁵	108	111	75		++	±	—	—	286	216	256		3.685	3.31	0.350	
	Slow ⁶	245	530	255	90	—	—	—	—	132	138	201	180	1.40	2.93	1.83	0.560
Ge.	Rapid ⁵	167	86	100		+++	+	—	—	280	113	204		3.66	2.52	0.48	
	Slow ⁶	275	99	94	82	—	—	+	—	55	158	188	246	0.64	2.63	2.86	0.776
Tu.	Rapid ⁵	180	108	52		±	++	—	—	238	x	x		3.32	3.45	0.560	
	Slow ⁶	228	132	110	60	—	—	—	—	192	151	150	99	3.04	2.22	1.75	0.310

¹ 1st 2-hour specimen

² 2nd 2-hour specimen

³ 3rd 2-hour specimen

⁴ 4th 2-hour specimen

⁵ 5.8 grams of sodium benzoate taken in powder wafers within 10 minutes

⁶ 5.8 grams of sodium benzoate, dissolved in 130 ml. water taken in 9 doses of 20 ml with 30 minutes interval

^{*} Ate a pear for luncheon

TABLE II shows the differences in the excretion of hippuric acid and benzoyl glucuronate when 5.8 grams of sodium benzoate is administered quickly or slowly. When 5.8 grams of sodium benzoate are ingested in the course of four hours the total quantity of hippuric acid excreted is just as large but the rate of excretion is slower than when this amount is ingested at one time. When 5.8 grams of sodium benzoate are taken in one dose the first 2-hour specimen usually contains more hippuric acid than the second 2-hour specimen. When the same amount is taken slowly over a 4-hour period, the second 2-hour fraction usually contains more hippuric acid than the first 2-hour specimen. The third 2-hour specimen which, after rapid ingestion of sodium benzoate usually contains only traces of hippuric acid,

curonic acid reactions in all fractional specimens of the urine. The same volunteers excreted considerable quantities of glucuronate after the rapid ingestion of 5.8 grams of sodium benzoate. Thus it is evident that as far as sodium benzoate is concerned, rapid absorption increases and slow absorption depresses the formation of benzoyl glucuronate. In view of the slow excretion of hippuric acid after ingestion of benzoic acid, this result seems to indicate that slow absorption from the intestinal tract is the main reason why the ingestion of benzoic acid is followed by the excretion of only small amounts of benzoyl glucuronate.

DISCUSSION

These observations may explain different discrepan-

cies reported in the literature.

Quick (11) had observed that the administration of benzoyl glucuronate to humans led only to the excretion of hippuric acid and no traces of the ingested benzoyl glucuronate were found in the urine. At the same time he found that whereas hippuric acid was eliminated rapidly after ingestion of sodium benzoate, hippuric acid excretion after benzoyl glucuronate was slow. Evidently, the benzoyl glucuronate must be hydrolyzed in the intestine before absorption. Absorption of benzoate

first 2-hour specimen usually contains more hippuric acid than the second. In the third 2-hour specimen the hippuric acid content is usually small.

After ingestion of 5 grams of benzoic acid the first 2-hour specimen contains never more — usually less — hippuric acid than the second. The third 2-hour specimen usually contains a considerable amount of hippuric acid. Individuals excrete more hippuric acid during the first two hours after the ingestion of 5.8 grams of sodium benzoate than in the first two hours

TABLE III

Average Excretion of Glucuronic Acid and Hippuric Acid after 5.8 Grams of Sodium Benzoate (Rapid and Slow Ingestion) and after 5 Grams of Benzoic Acid in 9 Normal Volunteers

	Naphthoresorcinol reaction				Glucuronic acid reduction in milligrams					Hippuric acid in grams				
	I ¹	II ²	III ³	IV ⁴	I ¹	II ²	III ³	IV ⁴	Total	I ¹	II ²	III ³	IV ⁴	Total
Na benzoate (Rapid)	+++	+±	—		305	206	155		666	3.76	2.74	0.280		6.815
Na benzoate (Slow)	—	—	±	—	174	184	201	170	559	2.17	2.92	1.65	0.352	7.17
Benzoic Acid ⁷	—	±	—		207	184	144		535	2.69	3.21	0.853		6.153

¹ 1st 2-hour specimen

² 2nd 2-hour specimen

³ 3rd 2-hour specimen

⁴ 4th 2-hour specimen

⁵ 5.8 grams of sodium benzoate taken in powder wafers within 10 minutes

⁶ 5.8 grams of sodium benzoate, dissolved in 180 ml. water taken in 9 doses of 20 ml with 30 minutes interval

⁷ 5 grams of benzoic acid taken in powder wafers within 10 minutes

is thereby delayed to such an extent that no formation of benzoyl glucuronate occurs.

Quick has stressed that about 75% of the sodium benzoate ingested by dogs is excreted as benzoyl glucuronate and only 25% as hippuric acid in contrast to the 7 to 10% of benzoate excreted as glucuronate in humans. In the liver of the dog no formation of hippuric acid takes place (12). Thus the dog's liver is always overwhelmed with benzoate after ingestion of this substance and a generous formation of benzoyl glucuronate results.

When Stricker introduced salicylate medication for the treatment of rheumatic fever in 1876 he used salicylic acid. Experienced clinicians like Naunyn and Minkowski (13) always maintained that salicylic acid was more effective in acute rheumatic fever than sodium salicylate. This contention sounds less incredible when it is realized that the metabolites formed after ingestion of an organic acid differ from those found after administration of the sodium salt of the same acid.

In some modern therapeutic uses of benzoic acid, pharmacological differences have been observed between the acid and its sodium salt; for example, benzoic acid is reported to be more effective in raising the penicillin level of the blood than sodium benzoate (14).

SUMMARY

After ingestion of 5.8 grams of sodium benzoate the

after ingestion of 5 grams of benzoic acid. This pattern of hippuric acid excretion indicates that the absorption of benzoic acid is slower than that of sodium benzoate.

After ingestion of 5.8 grams of sodium benzoate the first 2-hour specimen shows strong glucuronic acid reactions; in the second 2-hour specimen the glucuronic acid reaction is usually appreciable; in the third specimen the reaction is negative.*

After ingestion of 5 grams of benzoic acid the glucuronic acid reaction is always negative in the first and third 2-hour specimens. Only rarely is an appreciable reaction found in the second 2-hour specimen.

If 5.8 grams of sodium benzoate are administered in nine doses at half-hour intervals no excretion of glucuronic acid is observed.

These observations relate only to individuals with normal liver function.

CONCLUSIONS

Slow absorption of benzoic acid from the intestine, compared with the rate of absorption of sodium benzoate, might well explain the absence of glucuronate excretion* after intake of benzoic acid in normal persons.

*Examined with the method described on page 275.

REFERENCES

1. E. Salkowski: *Ztschr. f. physiol. Chemie*, 1:25, 1877.
2. A. Magnus Levy: *Biochem. Ztschr.*, 6:502, 1907.
3. J. Neuberg: *Biochem. Ztschr.*, 145:249, 1924.
4. A. Quick: *J. Biol. Chem.*, 67:477, 1927; 69:549, 1926.
5. A. Quick: *J. Biol. Chem.*, 70:59, 397, 1926; 80:535, 1928; 95:189, 1932; 96:83, 1932; 97:403, 1932; 98:157, 537, 1932.
6. J. Pryde and R. T. Williams: *Biochem. J.*, 27:1197, 1205, 1210, 1933; 30:794, 1936.
A. Quick: *Biochem. J.*, 28:403, 1934.
7. W. F. Goebel: *J. Biol. Chem.*, 122:649, 1938.
8. S. W. F. Hanson, G. T. Mills and R. T. Williams: *Biochem. J.*, 38:274, 1944.
9. A. Quick: *J. Biol. Chem.*, 98:537, 1932.
10. A. Quick: *J. Biol. Chem.*, 97:83, 403, 1932.
11. A. Quick: *J. Biol. Chem.*, 80:535, 1928.
12. G. Bunge, O. Schmiedeberg: *Arch. f. exper. Path. u. Pharmacol.*, 6:233, 1876.
I. Snapper, A. Grunbaum and J. Neuberg: *Biochem. Ztschr.*, 145:40, 1924.
I. Snapper and A. Grunbaum: *Klin. Wchnschr.*, 43:101-104, (Jan.) 1924.
A. Quick: *J. Biol. Chem.*, 96:73, 1932.
13. O. Minkowski: *Therap. der Gegenwart*, 10:385, 1908.
14. Bronfenbrenner, J. and Favour, C. B.: *Science*, 101:673, 1945.

Roentgenological Evidence of Appendiceal Abscesses

By

ARTHUR DALLOS, M.D.

NEW YORK, N. Y.

THERE ARE FEW REFERENCES in the literature relating to x-ray findings in appendiceal abscess. One of the earliest reports is found in the "Deutsche Medizinische Wochenschrift" of 1929, titled "Differential Diagnosis of the Acute Surgical Abdomen with the Help of the X-Ray" published by myself. This paucity of information is striking if you consider how decisive x-ray examination can be as an aid in proper diagnosis. The x-ray examination is important in any cases including those in which the diagnosis can be made by clinical examination. However, there are a number of obscure and clinically undiagnosed cases. These are patients where appendiceal abscess started weeks or months after their acute abdominal symptoms had subsided or in which the patients could not recall any acute abdominal illness. These are cases of a chronic type in which as a result of a suppurative infection the appendix has been perforated and become walled off producing a localized abscess with tumor formation.

Before enumerating the x-ray signs most commonly seen in the picture of appendiceal abscesses several interesting x-rays of some of my own cases are illustrative. The most important points of the history, surgical procedure and after-course follow as well.

As illustrative case, No. 1 is that of a 46 year old white male. The diagnosis was clinically evident. Five days before examination he suffered a slight attack of indigestion and abdominal distress. At examination there was a palpable mass in the right lower abdomen. There was no fever, his white count was 13,500 with 82 polys. X-ray barium enema was done, the findings were: a mass about the size of a lemon at the ileocecal region, causing indentation of the tip of the cecum. This is a definite indication of the presence of a mass either abscess or tumor. Abscess is quite probable. Operation revealed a large appendiceal abscess which was opened and drained. The appendix was gangrenous but could be removed. Post-operative course was uneventful.



Case 1 — Case of appendiceal abscess. Barium enema.

Case No. 2 offered a problem from the diagnostic point of view. Again, a white male patient, 46 years old. His sickness started at the end of July 1944, with lack of appetite and a general run-down status. He was sent by his family doctor to an x-ray man on August 12, 1944. G. I. series revealed the following picture, film no. 2 and were reported as negative. On August 18, 1944 the patient suddenly became acutely ill with a temperature over 100 and a palpable mass in the right lower abdomen. He was taken to the hospital



Case 1 — Same case after evacuation.



Case 2 — Same case two days after acute illness started. Barium enema (Film No. 3A).



Case 2 — Cecal region of G. I. Series, about three weeks before acute illness started (Film No. 2).



Case 2 — Same case after evacuation (Film No. 3B).



Case 2 — Same case three months post-operative. Barium enema (Film No. 4A).

on August 22nd with an admission temperature of 101, a sedimentation rate of 25 mm. in one hour and a white count of 9500 with 72 polys. I quote the findings of the x-ray examination at that time (film no. 3). "Near the ileocecal wall there is a constant uneven scalloped filling defect, suggesting the presence of an obstructive mass. Differential lies between an intrinsic tumor of the bowel or an extrinsic mass such as abscess creating pressure and obstructive defect. Interpreted with submitted films of a G. I. series there is a certain unevenness with sharp margins that favor an intrinsic tumor of the bowel, most probably carcinoma." Operation on August 25th, 1944, revealed a big inflammatory mass in the right abdomen with edema and fibrin around the tumor. Tapping of the tumor produced only a very small amount of pus. Careful insertion of an abscess-forceps into the abscess did not reveal more pus. It was not possible to state the origin of this inflammation, whether it was a broken-down carcinoma or an organized appendiceal abscess. Because of the obstructive lesion a typical short circuit operation, an ileotransversostomy, was performed. In addition the tumor region was drained. Recovery was satisfactory, with a gradual subsidence of fever and healing of the wound. Patient discharged subsequently on September 16th, 1944. During wound healing one large fecalith was sloughed from the wound. The palpable mass in the right abdomen subsided totally and x-ray examination three months later, in October, shows the cecum to be completely restored (film no. 4). There cannot be any doubt that



Case 2 — Same case after evacuation (Film No. 4B).

this case was an appendiceal abscess and not a broken-down carcinoma.

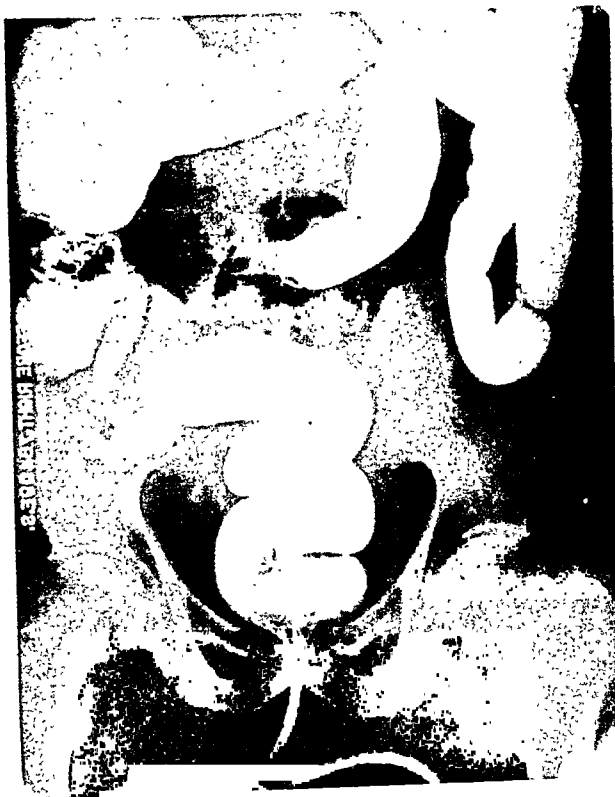
This third case was that of a 54 year old white male. History: Three months ago patient suffered a gall-bladder attack twice. For three weeks before examination he ran elevated temperatures in the evening while morning temperatures were normal. At the same time he lost appetite and energy and became tired and weak. His chief complaints were anorexia, feeling of fever and weakness. He was under observation for three weeks in a hospital and was seen by several prominent consultants. He was tested for typhoid and Bang, received penicillin without improvement, several blood cultures were taken with no final diagnosis. A colon series which was presented to me at the time of my first consultation was inefficient from a technical point of view. Physical examination revealed tenderness in the right loin on very deep palpation. Sedimentation rate was 62 mm. in one hour, white count 14,000. I quote the x-ray report (film no. 5): "The ascending portion of colon is spastic with marked irregular filling defects. Conclusions: Irregular narrowing of the mid-ascending portion of colon with tenderness and fixation suggesting the presence of an angular malignancy." Exploration revealed a very swollen and thickened retrocecal appendix. Around the tip of the appendix contiguous with the serosa of the cecum were masses of granulation tissue, the remainder of an appendiceal abscess in the stage of absorption. Appendectomy was done, sulphanilamide powder distributed around the



Case 3 — Appendiceal abscess. Barium enema (Film No. 5A).



Case 3 — Same case after evacuation.



Case 3 — Same case after evacuation (Film No. 5B).



Case 3 — Same case few months post-operatively. Barium enema (Film No. 6).



Case 4 — Appendiceal abscess. Barium enema (Film No. 7).

area of granulation tissue and one cigarette drain inserted. Speedy recovery ensued with return of the white count and sedimentation rate to normal. X-ray examination of December 19th, 1944, revealed a normal cecum (film no. 6).

The last two cases represent twin brothers aged 21. One of the brothers became ill while in military service, complaining of dizziness, weakness and loss of appetite. Because of a tumor in the ileocecal region diagnosed by x-ray examination he was medically discharged from the service at his request to be operated by the same surgeon who had operated on his twin brother for a similar condition eight months earlier. On admission tenderness on deep pressure in the right lower quadrant was evident. I quote the x-ray findings (film no. 7). "Oral and rectal examination of the ileocecal area reveals a constant stricture above the lower cecum pole measuring almost 2 inches in length. There is a delayed evacuation of the ileum with congestion of its terminal loop. Findings are highly suggestive of an ileocecal tuberculosis." Operation on June 14th revealed a very swollen retrocecal appendix, the cecum showed an inflammatory condition with tumor formation. It was not possible to decide with certainty whether this condition was the result of an appendicitis or tuberculous process. Therefore an ileocecal resection was done. The report of the pathologist revealed only an acute exacerbation of a chronic appendix with multiple mucosal polyps of the



Case 4 — Same case after evacuation (Film No. 7B).

cecum. The inflammatory condition of the cecal mucosa was without doubt a reaction to the appendiceal process.

The twin brother was admitted to the hospital on October 19th, 1942, having had irregular stools, alternating constipation and diarrheas with considerable loss of weight and pain in the right abdomen. Operation revealed a large inflammatory tumor involving the cecum, ascending colon and terminal loop of ileum. All glands of the meso-colon were very much enlarged. (X-ray films of this case with filling defects as in the other cases unfortunately lost.) An ileotransversostomy was the operation of choice, post-operative an uneventful course. Discharge was on the 16th day of operation. Speedy recovery with disappearance of the tumor in a very short time. I would like to emphasize that my own impression on all of the x-rays shown above, against the opinion of the x-ray specialist, was: No malignancy, probably appendiceal abscess.

- (1) Filling defects, either extrinsic or intrinsic or both;
- (2) Fixation of cecum and last loop of ileum;
- (3) Elevation and displacement of ileum;
- (4) Hyper-irritability and hyper-motility with cecal spasm;
- (5) Sensitiveness and tenderness of the area;
- (6) No visualization of the appendix.

The surgical procedure must be decided at the operation itself. In the above cases, one had an appendectomy, one appendectomy with drainage of abscess, two ileotransversostomy and one an ileocecal resection.

On closing, I would like to mention the differential diagnosis of this area:

- (1) Carcinoma of cecum;
- (2) Ileocecal Tuberculosis;

- (3) Regional ileo-colitis;
- (4) Actinomycosis;
- (5) Invagination with Intussusception.

Other conditions, outside of the intestines, such as pelvic abscess originating from the adnexae and paranephritic abscess are worth considering.

Attention to the x-ray findings in appendiceal abscess can be very useful in making a diagnosis in conditions involving right lower quadrant.

The Fasting Gastric Contents as an Index of Gastric Functioning

By

FREDERICK HOELZEL

CHICAGO, ILL.

ABOUT TWENTY YEARS AGO, I became convinced that appropriate observations on the fasting gastric contents yield the most reliable data obtainable concerning the natural gastric secretory and motor activity. I assumed that the findings reported in my first paper concerning the work of the fasting stomach (1) made the value of observations on the fasting gastric contents self-evident but apparently this was not the case. In the meantime, the value of the commonly used or older tests of gastric function has repeatedly been questioned and newer tests, based on the same old or equally questionable principles, have been proposed. It therefore seems worth explaining, in more or less detail, how and why I became convinced that appropriate observations on the fasting gastric contents yield the most reliable data obtainable concerning natural gastric functioning.

I began making observations on my fasting gastric contents early in 1925 to determine whether the fasting gastric acidity was a factor influencing the epigastric hunger sensations and whether the gastric acidity was a factor determining the craving or appetite for protein. Earlier attention to hunger, under various nutritional conditions, led me to believe that there were specific hungers, such as, protein hunger, carbohydrate hunger, etc. (2). The gastric "hunger contractions" did not seem to explain protein hunger but I thought that protein hunger might be due to the titillation or peptic irritation of the gastric mucosa by highly acid fasting gastric contents and that the appeasement of protein hunger by ingested protein might be explainable by the acid binding power of protein. In any case, when this study was begun, the chief problem seemed to be to avoid interfering with the manifestation or recognition of relatively vague variations in my epigastric and general hunger sensations while securing data concerning the acidity of the fasting gastric contents. Hence, I made gastric aspirations at first only after epigastric hunger sensations were clearly noted and I aspirated only

enough of the fasting gastric contents to facilitate the determination of the acidity. To obtain a representative fraction of the fasting gastric contents, they were, however, first mixed a little in the stomach by alternately applying gentle suction and blowing and, when the stomach was found to be practically empty, enough of the fasting gastric secretion was obtained to serve in place of a fraction of the commonly found fasting gastric contents. Only 1 determination of the gastric acidity was made during each period of subjectively recognized gastric "hunger contractions" and, consequently, only 2 or 3 determinations could be made during 6 to 8 hours of more or less continuous observation, as the periods of "hunger contractions" were often 3 hours apart. To employ the time to better advantage, I therefore next also made 1 determination of the gastric acidity during each period of subjectively recognized fasting gastric motor quiescence between the periods of "hunger contractions."

As a result, considerable differences in the fasting gastric acidity were found in successive determinations made on the same day and only from 1 to 2 hours apart. Considerable differences in the volume of the fasting gastric contents were also indicated by differences in the ease or difficulty with which the desired gastric fractions were obtainable. It therefore seemed of interest to determine the volume of the fasting gastric contents as well as the acidity. Hence, complete aspirations were next made and I tried to maintain or restore the natural gastric conditions as nearly as possible by returning almost all of the aspirated fasting gastric contents, by tube, to the stomach after the volume was noted. Only 1 cc. was reserved for titration. When the acidity and volume of the fasting gastric contents were thus determined at approximately half-hourly intervals orderly periodic changes were usually found.

However, in this connection the importance of taking precautions to avoid altering the natural gastric functioning became emphasized. That is, the complete aspirations were at first made into a simple aspiration

bottle which served well enough when only partial aspirations were made but the completely aspirated fasting gastric contents then had to be transferred to a graduate to measure the volume. Next, 1 cc. was separated to be reserved for titration. The intention was to return the balance of the aspirate to the stomach by pouring it into a funnel attached to the aspiration tube but no funnel with a stem small enough to fit the regular aspiration tube was available at first. A larger tube with a funnel attached was therefore used to return the material. Thus the return of the aspirated fasting gastric contents was evidently delayed too much and they also became chilled (in winter). Moreover, the return of the aspirate through the larger tube was very likely too rapid to permit any rewarming in the esophagus and too abrupt to prevent an artificial stimulation of the fasting gastric motor activity. The natural periodic fasting gastric motor and secretory activities were apparently altered as a consequence on some occasions. Such alteration of natural gastric functioning seemed to be averted by making the aspirations directly into a stoppered graduate and, after noting the volume, immediately, but not too abruptly, returning unneeded amounts of the aspirate through the regular aspiration tube by simply raising and tilting the graduate.

The general findings with the use of the latter technique were previously described (1, 3). In short, it was found that the secretions (acid gastric juice, gastric mucus and swallowed saliva) accumulated in the stomach during the periods of practical motor quiescence. They were discharged into the duodenum during the periods of increased gastric tonus and motor activity. The "hunger contractions" were clearly felt only when the stomach was practically empty. The acidity of the fasting gastric contents tended to be highest during periods of high gastric tonus and motor activity and lowest during the periods of low tonus and motor quiescence. An inverse relation between the acidity and volume of the fasting gastric contents therefore usually existed. Gastric mucus was found to be secreted mainly after the "hunger contractions" occurred and an inverse relation between mucus secretion and acid secretion seemed to exist. Bile contamination of the gastric contents (duodenal regurgitation) occurred intermittently, but not always, during periods of emptying of the stomach and apparently only after discharged acid gastric contents irritated the duodenum. Curves showing the changes in the acidity and volume of the fasting gastric contents suggested that the fasting gastric contents served like a test meal in revealing the basal level and pattern of gastric functioning. Moreover, the level and pattern of fasting or basal gastric secretory and motor activity was lower than, but otherwise seemingly parallel to, the level and pattern of the digestive (that is, stimulated) gastric activity.

That the repeated aspiration and (careful) return of the fasting gastric contents at half-hourly intervals did not significantly alter the fasting gastric functioning

was indicated in several ways. First, the acidity and volume found at the first aspiration made on any day (before any preceding return of aspirated fasting gastric contents) was often the same as, or (as will be explained later) only slightly higher than, the acidity and volume found at similar phases of the periodic cycles of fasting gastric secretory and motor activity observed after the repeated aspiration and return of the fasting gastric contents. Second, the intervals between the periods of "hunger contractions" were not altered. And third, the epigastric hunger sensations were apparently not changed although they are changed by continuous aspiration and by the balloon method of studying the fasting gastric motor activity (3).

The finding of periodic variations in the acidity of the fasting gastric contents raised the question whether they were partly or largely due to variations in the rate of secretion. Some tests on the rate of secretion were therefore made by means of continuous aspiration. Evidence was found and previously published (1) indicating that the acidity varied independently of the rate of secretion. However, since I reported this finding, Bloomfield, Chen and French (4) claimed that the "basal gastric secretion" usually became approximately constant in rate and acidity within 60 minutes of continuous aspiration. Figure 1 is therefore presented to show what I found in 1925 when I happened to determine the acidity and volume of the fasting gastric secretion obtained by continuous aspiration in 10-minute intervals as suggested by Bloomfield, Chen and French. It can be seen that the acidity and rate of secretion seem to be constant during some successive 10-minute intervals but they do not remain constant. The prolonged observations of Hellebrandt and her associates (5), as well as my observations, indicate that the fasting gastric secretion varies periodically. Continuous aspiration does not abolish the periodicity but it seems to distort it and it incidentally changes the epigastric hunger sensations. Observations on the "basal gastric secretion" obtained by continuous aspiration were therefore worthless for my investigation of the relation between the fasting gastric acidity and epigastric hunger sensations. It would seem obvious that this would likewise apply to any attempt to determine the relation between fasting gastric functioning and the occurrence of ulcer pain. The finding of Bloomfield, Chen and French (4) that the secretion obtained by continuous aspiration is a much more sensitive index of gastric function than the response to histamine is nevertheless worth emphasizing. It supports my own conviction that the fasting gastric contents serve as the most sensitive as well as the most reliable index of natural gastric functioning.

Another question raised early in my study concerned the effect of swallowed saliva and regurgitated duodenal contents on the acidity of the fasting gastric contents. The only time that I tried to avoid swallowing saliva was immediately before and during intubation. The aspiration tube was always removed between the inter-

mittent (generally half-hourly) aspirations. This was done to minimize the stimulation of the flow of saliva and the possible stimulation of the secretion of gastric juice and also to minimize interference with the manifestation and recognition of vague differences in the epigastric hunger sensations. My practice however also became to swallow a little saliva deliberately immediately after the aspiration tube was removed, between each half-hourly aspiration. This was done to counteract the acid drawn into the esophagus by withdrawing the tube. Before this was done, the esophagus occasionally became eroded and bled a little at the cardia after a large number of aspirations were made on successive days. The moderate amounts of saliva that were swallowed deliberately or spontaneously between aspirations

gastric secretion. It follows from this that the removal and withholding of the fasting gastric contents is likely to distort gastric functioning. In any case, I was interested in the gastric acidity under normal or natural conditions, involving the swallowing of spontaneously secreted saliva, and it would seem that clinicians would also be interested in securing their data under natural conditions. Duodenal regurgitation likewise appears to be normal under some conditions although such conditions may not be ideal (3). Transient reductions in the gastric acidity by duodenal regurgitation should therefore be regarded as part of the evidence of natural basal gastric functioning. The rapidity with which the acidity increases again after duodenal regurgitation is often a good index of the secretory potential. In this

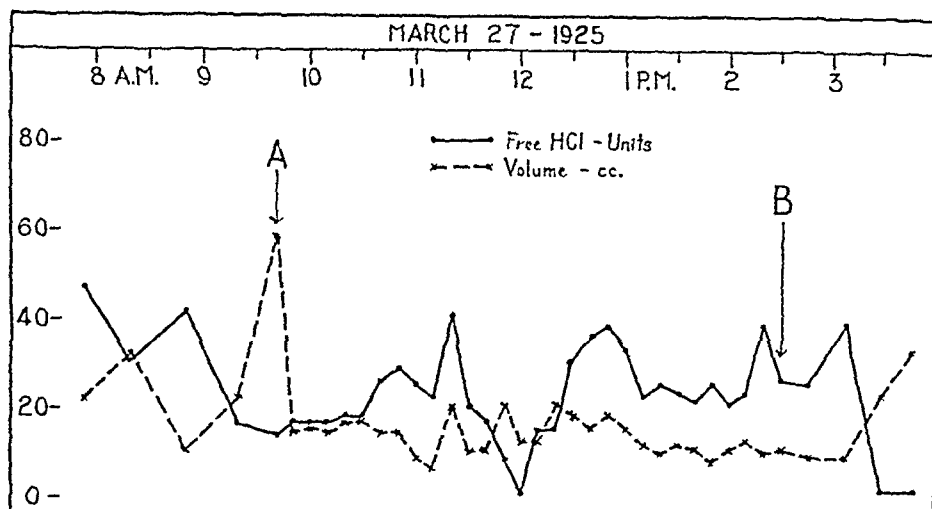


Fig. 1 — Showing that the acidity and volume of the fasting gastric secretion obtained in 10-minute intervals by continuous aspiration (between A and B) were not constant. Before A and after B, aspirations were made only at 20- to 40-minute intervals and all but 1 cc. of the aspirated fasting gastric contents was promptly returned to the stomach after each aspiration. At A, the aspirated fasting gastric contents were withheld.

did not seem to lower the gastric acidity. The regurgitation of duodenal contents, as indicated by bile contamination of the gastric contents, also appeared to lower the gastric acidity only transiently. An explanation of this was found when the acidity of the fasting gastric contents was either lowered or raised artificially by adding a small amount of a relatively strong solution of NaOH or HCl to the aspirated fasting gastric contents before they were returned to the stomach. Whenever the acidity was lowered by adding NaOH, the acidity was always found to be increased again 15 to 30 minutes later. Whenever the acidity was increased by adding HCl, the acidity was always found to be decreased again 15 to 30 minutes later. But when the acidity was left unchanged, it was usually found to be either increased or decreased 15 to 30 minutes later, depending on the phase of the natural cycle of periodic change in acidity in which the observations were made. These results indicate that the acidity and presumably also the other properties of the fasting gastric contents are factors influencing the fasting or natural basal

connection it should however be borne in mind that the influx of duodenal contents into the stomach may sometimes be increased artificially by the suction used in aspirating the gastric contents.

As indicated in previous papers (1, 3) and earlier in this paper, the major periodic variations in the acidity of the fasting gastric contents are evidently due to periodic increases in the secretion of gastric mucus and inverse changes in the acid secretion. The periodic increase in the gastric mucus secretion seems to be due to irritation of the gastric mucosa by the periodic gastric "hunger contractions" but the amount of mucus secreted also appears to depend on nutritional factors (3). The major and minor changes that were found to occur in the acidity of the fasting gastric contents suggested that only the average acidity during a period of sufficient length could be regarded as the representative acidity for any day. Theoretically, this meant the average acidity during at least one complete periodic cycle of the fasting gastric secretory and motor activity. In practical terms, this generally meant the average of 6

or 7 half-hourly determinations of the acidity of the fasting gastric contents as my "hunger contraction" periods were often 3 hours or a little more than 3 hours apart. Half-hourly intervals were preferred for making the determinations of the acidity and volume of the fasting gastric contents because they usually served

tein intake was varied. For this purpose, successive changes or contrasts in protein nutrition seemed best. It was soon found that protein restriction increased the average gastric acidity and protein re-alimentation or an excessive protein intake reduced the average gastric acidity (6). Moreover, as an apparent result of the high

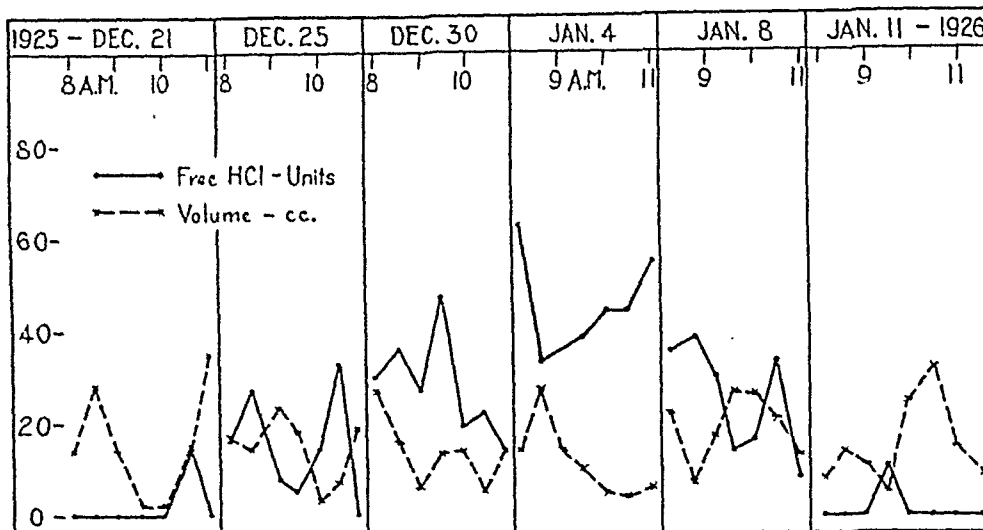


Fig. 2 — Changes produced in the acidity and volume of the fasting gastric contents in 3- to 5-day intervals by a restriction of the protein intake (between Dec. 21 and Jan. 4) and by a liberal protein intake (between Jan. 4 and Jan. 11).

to reveal all of the major changes and they left sufficient time between the aspirations to permit adequate observation of the epigastric and general hunger sensations.

As my study of the work of the fasting stomach was

gastric acidity produced by rigid protein restriction, a specific type of epigastric hunger was found to develop (7). However, the changes in the acidity (and volume) of the fasting gastric contents produced by changes in the protein intake usually became evident

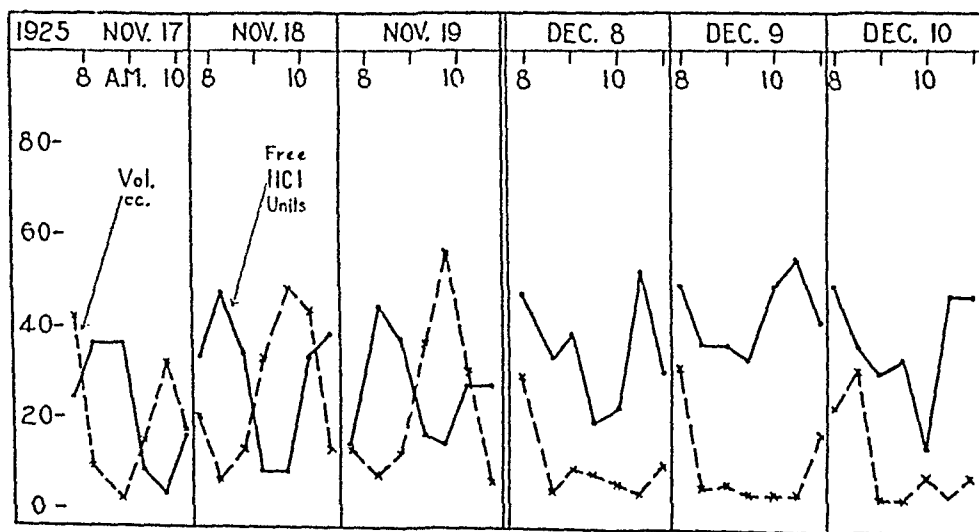


Fig. 3 — Similarities in the acidity and volume of the fasting gastric contents found on 3 successive days during 2 periods. Nov. 17, 18 and 19, a period with intermediate or practically normal gastric acidity. Dec. 8, 9 and 10, a period of high gastric acidity at the end of a period of protein restriction.

not primarily undertaken to find and promote a new test of gastric function, no special attempt was made to determine whether the method which I used would yield similar results under similar conditions in repeated tests. My aim rather was to determine whether the method would reveal differences in gastric functioning and in the epigastric hunger sensations when the pro-

only after 3- to 5-day intervals (Figure 2). On some successive days, practically no change was revealed, as indicated in Figure 3. In short, results like those in Figure 3 practically supplied proof that similar results are obtainable under similar conditions. On the other hand, the differing curves in Figures 2 and 3 show that similar results are not obtainable on the same individ-

ual unless all conditions likely to influence gastric functioning are kept constant. This was also emphasized by Helebrandt and Brogdon (8). In the course of my study, it was occasionally noted that the mere presence of an excessive amount of gas in the lower bowel disturbed gastric functioning.

The method of making multiple half-hourly observations which I used to obtain data like those upon which Figures 2, 3 and 4 are based was evidently necessary to establish the fact that the fasting gastric contents serve as a reliable index of gastric function but this method is apparently too cumbersome to be used as a general purpose test of gastric function. However, I found that a number of single (daily, weekly or otherwise isolated) determinations of the acidity, volume and other characteristics of the fasting gastric contents can also be of considerable value. Single determinations are easily made because it is not essential to return the bulk of the aspirated fasting gastric contents to the stomach or to do this with care when it is not intended to make another determination within a few hours and no time need be lost in waiting between aspirations as when half-hourly aspirations are being made. The value of a number of single determinations of the acidity of the fasting gastric contents became evident in my experience only, by accident. That is, after having made about 2000 aspirations on myself mainly by the multiple half-hourly method, I discontinued this practice in 1926 because it was cumbersome and nothing new seemed to be revealed. Nevertheless, I continued making at least 1 determination of the fasting gastric acidity daily, shortly after rising, and largely as a further check on previous observations. Making 1 aspiration each morning to determine the gastric acidity became a mere routine by 1928 when an episode occurred which upset me greatly emotionally (9). The extent to which I was upset was apparently best indicated by the fact that my gastric acidity, as revealed by the routine single daily determinations, became about twice as high as the highest observed before or afterward under similar nutritional conditions. This convinced me that the finding of an unusually high acidity in a single or a few single (daily or otherwise isolated) observations on the fasting gastric contents could be highly significant but it was 14 years later before I fully appreciated the significance of some unusually low acidities which were revealed by the single daily determinations already before 1928.

I made no observations on my gastric acidity between 1929 and 1942 but I again began making single daily determinations of the acidity (and volume) of my fasting gastric contents in 1942 because of a number of developments and considerations. First, reports of an increase in peptic ulceration in war torn Europe revived previous interest in this subject (10) and led me to report my observation of the effect of fear on gastric acidity (9). Second, it seemed worth determining whether the war rationing of food or possible food shortages would increase the gastric acidity and help

explain the increased ulceration in wartime as a consequence of nutritional changes. Third, I had adopted the practice of fasting 1 day each week and it was of interest to determine its effect on the gastric acidity. In addition to this, 25 years had elapsed since observations were first made on the secretory activity of my fasting stomach (2) and I was interested in determining whether clear evidence of changes would be found. If the desirability or necessity became apparent, I also intended to make multiple (half-hourly) observations but it became obvious that single daily determinations would serve my purpose when this method revealed that the gastric acidity was distinctly lowered by my single-day or weekly fasts (11). The results then led to a reconsideration of data obtained between 1925 and 1929 and interrelations between nutrition and gastric functioning were found which I previously either failed to note or misinterpreted (12, 3).

The use of data obtained by single (daily, weekly or random) determinations of the acidity of the fasting gastric contents naturally raised the question concerning the relative value of such data when compared with the average of about 6 or 7 half-hourly determinations. Figure 4 shows the averages of 5 to 9 daily determinations of the acidity of the fasting gastric contents and also the results of single (the initial) daily determinations. It can be seen that the results of some single or initial determinations diverge widely from the average of the 5 to 9 determinations but a rough general agreement can also be observed. Obviously the average of a few single daily determinations would correspond more closely with the grand average of multiple determinations made on the same days. However, the volume, mucus content and degree of bile contamination of the fasting gastric contents often reveal the phase of the periodic cycle of fasting gastric secretory (and motor) activity during which the aspiration was made and this, under normal conditions, indicates whether the acidity is likely to be near the average or is likely to diverge considerably from the average. Most commonly, the acidity and volume of the fasting gastric contents are inversely related, as indicated in Figure 3 (Nov. 17, 18 and 19). Uncertainties concerning the phase of the periodic fasting gastric secretory cycle during which an aspiration has been made can usually also be dispelled by returning the bulk of the aspirated fasting gastric contents and making 1 or 2 additional observations at half-hourly or other intervals.

Figure 4 incidentally shows that the initial gastric acidity was often higher and rarely lower than the average of the 5 to 9 determinations that were made daily. This proved to be contrary to earlier general impressions. That is, my impression was that the gastric acidity usually rose toward the end of the somewhat tedious observation periods and that the data then obtained were complicated by the development of more or less of an appetite gastric secretion. However, a detailed analysis of the data for the period represented in

Figure 4 showed that the average initial acidity was higher than the average final acidity. The acidity here considered as the "final acidity" does not include the acidity found after deliberate attempts were made to induce an appetite secretion. Both the initial and the final acidity were (on the average) higher than the average. In other words, the average acidity first decreased and then again increased during a few hours of observation in the morning. Without further study, an explanation of the changes is necessarily somewhat speculative. However, I believe that the relatively high acidity of the fasting gastric contents found at the first determination (which was usually made within 15 minutes after rising) represented the effect of a nocturnal

would further seem that tension due to fear or other factors influences the fasting gastric secretion through the same mechanism.

The data obtained by the daily determinations of the acidity and volume of my fasting gastric contents between 1942 and 1944 suggested that there was some decrease in the gastric acidity since 1925 but this decrease seemed to be of questionable significance. A distinct decline in gastric functioning was nevertheless indicated by a marked decrease in the apparent rate of secretion. That is, if the rate of (mucus and acid) secretion had remained unchanged, the average and maximum volume of the fasting gastric contents should have been increased as tests with the balloon method of re-

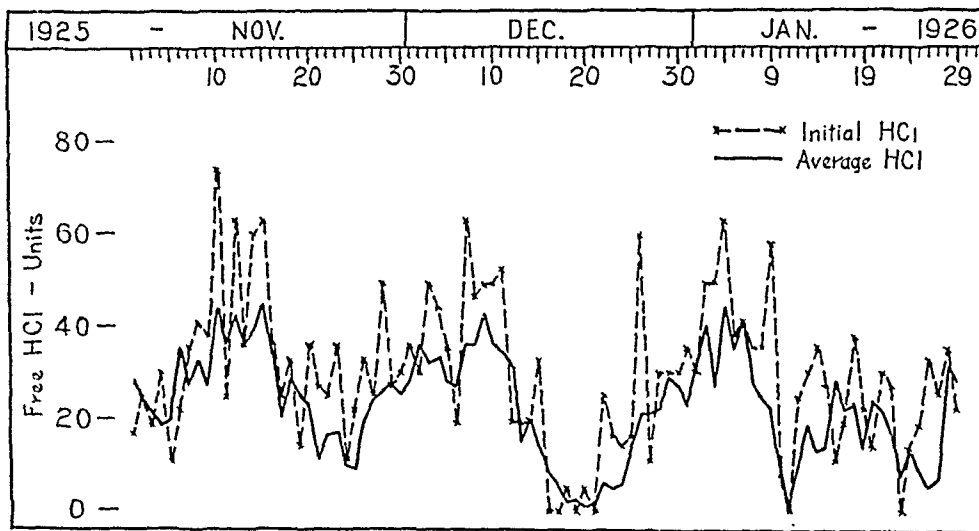


Fig. 4 — Showing the average of 5 to 9 daily (half-hourly) determinations of the acidity of the fasting gastric contents and the acidity found at the first of the 5 to 9 daily determinations. The major changes in the acidity during this period were produced by variations in the protein intake.

secretion relatively high in acidity and that the nocturnal fasting acidity tends to be relatively high because of the effect of the recumbent position on the blood or fluid supply to the stomach. After rising, the upright position presumably reduces the blood or fluid supply to the stomach and hence the rate and acidity of the fasting secretion decreases. This and some general dehydration would explain a decrease in the acidity and volume of the fasting gastric contents. The increase in acidity which became apparent with the lapse of time was evidently due to an increasing hunger or basal appetite secretion. A hunger or basal appetite secretion, centrally mediated (13), is a necessary basis for the development of an acquired appetite secretion (a gastric response to the thought of eating specific foods). This is very likely the neurogenic fraction of the fasting gastric secretion which can be reduced by atropine. As hunger seems to involve more or less tension, it

corded the gastric motility as well as subjective observations indicated that my fasting gastric tonus and motor activity had decreased. The maximum volume found between 1942 and 1944 was however only 43 cc. while 70 to 90 cc. were not uncommonly found in 1925. This suggests that the rate of the natural basal gastric (mucus and acid) secretions decreased 50% or more in less than 20 years (between the ages of 36 and 55). Simultaneous decreases in the secretion of mucus and acid would explain why the acidity was not clearly decreased. It might be added here that the food supply during the war never became restricted enough to increase the gastric acidity.

The foregoing would seem to be ample evidence that appropriate observations on the fasting gastric contents yield as reliable and valuable data as can be obtained concerning natural gastric functioning.

REFERENCES

1. Hoelzel, F.: The relation between the secretory and motor activity in the fasting stomach (man). *Amer. J. Physiol.*, 76:463, 1925.
2. Carlson, A. J.: Contributions to the physiology of the stomach. XLV. Hunger, appetite and gastric juice secretion in man during prolonged fasting (fifteen days). *Amer. J. Physiol.*, 45:120, 1918.
3. Hoelzel, F.: An explanation of appetite. *Amer. J. Dig. Dis.*, 11:71, 101, 1944.
4. Bloomfield, A. L., Chen, C. K. and French, L. R.: Basal gastric secretion as a clinical test of gastric function with special refer-

ence to peptic ulcer. *J. Clin. Invest.*, 19:863, 1940.

5. Hellebrandt, F. A.: The relation between the motor and secretory functions of the human fasting stomach. *Amer. J. Physiol.*, 112: 162, 1935. Hellebrandt, F. A., Tepper, R. H., Grant, H. and Catherwood, R.: Nocturnal and diurnal variations in the acidity of the spontaneous secretion of gastric juice. *Amer. J. Dig. Dis. and Nutrition*, 3:477, 1936.
6. Hoelzel, F.: The effect of variations in protein intake on the acidity of the secretion of the fasting stomach. *Amer. J. Physiol.*, 77:166, 1926.
7. Hoelzel, F. and Kleitman, N.: Some conditions affecting subjective and objective manifestations of hunger. *Arch. Int. Med.*, 39:710, 1927.
8. Hellebrandt, F. A. and Brogdon, E.: The validity of fractional

gastric analysis. *Amer. J. Dig. Dis. & Nutrition*, 2:402, 1935.

9. Hoelzel, F.: Fear and gastric acidity. *Amer. J. Dig. Dis.*, 9:188, 1942.
10. Hoelzel, F. and Da Costa, E.: Experimental production of pylorospasm and gastric retention in rats. *J. Exper. Med.*, 57:597, 1933. Production of peptic ulcers in rats and mice by diets deficient in protein. *Amer. J. Dig. Dis. & Nutrition*, 4:325, 1937.
11. Hoelzel, F.: Relation between nutritional hydration and the contents of the fasting stomach while fasting one day per week. *Gastroenterology*, 1:970, 1943.
12. Hoelzel, F.: Gastric acidity, nutritional hydration and appetite. *Amer. J. Dig. Dis.*, 10:121, 1943.
13. Hoelzel, F.: Central factors in hunger. *Amer. J. Physiol.*, 82: 665, 1927.

Gastrosocopy as an Aid to Diagnosis of Gastric Disorders*

By

A. N. ROSSIEN, M.D.**

KEW GARDENS, N. Y.

INTRODUCTION

I AM ABOUT TO DISCUSS with you a subject that is becoming more and more recognized as having considerable merit in the diagnosis of gastric diseases. As in all new ventures, there are those who persist in refusing to recognize its value and also those who go so far as to claim for it values beyond its possibilities. Neither of these extreme views are scientific. Errors of interpretation, due to limitations, can be made on gastroscopic study just as they may be made with any other method of study. Each method has its limitations and advantages. The correlation of the observations made by all of the methods available lead to less errors in diagnosis. That and that alone should be our primary purpose.

Gastrosocopy is only an adjunct in the study of the stomach. It is not intended for nor must it be used to the exclusion of all other methods of examination. Actually, this method of examination should not be resorted to before the conventional means of diagnosis have been used. Before a gastroscopic interpretation is made, the findings should be correlated with the history, physical examination and x-ray and laboratory observations. Gastrosocopy should never be used before an x-ray study of the oesophagus and gastric cardia reveals that there are no obstructions. If there are no contra-indications, gastroscopic examination may confirm the previous diagnosis or bring to light hitherto unsuspected pathological lesions.

As I shall point out later, there are various conditions of the stomach that on x-ray cast shadows resembling each other and at times may not even be visualized. The gastroscopist, in many instances, can differentiate

these shadows. Mind you, I am not trying to perpetuate the discussion of "X-ray versus Gastrosocopy." That type of discussion would be as futile and unproductive as a discussion of, let us say, "The Internist versus The Pathologist." X-ray and gastroscopy both have their places in the armamentarium for medical diagnosis. Roentgenologists and gastroscopists must not necessarily merely seek to graciously complement each other; but, that they should supplement, not substitute, each other, there no further can be any doubt. Thus, as in all other medical studies, the pathological entities of the living stomach will become more and more clarified.

HISTORY

This method of examination had been attempted for many years and for various reasons had met with failure. However, each of the pioneer workers contributed some information to the present gastroscopists, thereby making the procedure and interpretation considerably easier. No doubt, much remains to be learned in this field as well as in all of the other branches of medicine.

Kussmaul, in 1868, advanced the knowledge for gastroscopists with his observation that lamp illumination at the mouth was insufficient. He, further, suggested that a flexible gastroscope would tend to minimize the danger associated with the passing of the instrument.

It remained for Nitze and Leiter, in 1879, to reason correctly that the instrument of choice for visualization would be one with a cystoscope-like arrangement of lenses. The electric lamp had not been invented at that time. Hence, Nitze and Leiter were obliged to use electricity to heat platinum wires that were in their gastroscope. The heat thus generated resulted in light rays being cast on the gastric mucosa. The mucosa, in turn, reflected the rays of light to one of the lenses. These reflected rays were brought up to the examining eye through a series of lenses. However, a constant stream of water had to be circulated to cool the instrument. Unlike the urinary bladder, the stomach is best visualized through a medium of air, not water. This

*First of a series of ten lectures on gastroenterology delivered Nov. 9, 1945 under the auspices of the Educational Committee of the Medical Society of The County of Queens, New York.

**Consultant Gastroenterologist, Rockaway Beach Hospital; Attending Gastroenterologist, Triboro Hospital; Associate Visiting Physician (Gastroenterologist) Queens General and Jamaica Hospitals.

Consultant Gastroenterologist, Long Beach Hospital.
Assistant Chemical Professor of Medicine, New York Medical College.
Flower and Fifth Avenue Hospitals.
Submitted February 13, 1946.

factor plus the cumbersomeness of their rigid instrument and the dangers obviously involved made it unsatisfactory.

Mikulicz, in 1881, constructed a rigid instrument 65 cm. in length with a 30 degree angulation at the juncture of its middle and lower third. By the construction of his gastroscope, Mikulicz indirectly provided the anatomical explanation for Kussmaul's suggestion of the need for a flexible gastroscope. Schindler (1) states that that instrument indicated that Mikulicz must have been aware of the following facts:

(a) "The axis of the stomach forms a marked angle with the axis of the oesophagus." (Rosenheim, in 1895, substantiated this with his finding that the last 3 cm. of the cesophagus were directed to the left, thereby resulting in angulation with the stomach.)

(b) "The lower pole of the stomach turns towards the anterior abdominal wall."

(c) "The greater curvature of the stomach does not descend vertically, but the plane of the stomach is twisted and curved in a complicated manner."

Schindler and Wolf coordinated the work of the pioneers and with some original additions produced a flexible gastroscope which conforms to the needs for gastroscopy. Recently the Cameron Surgical Specialty Company made additions to gastroscopy by means of their Omniangle Gastroscope. I find this instrument most helpful.

BLIND SPOTS

There still remain areas of the stomach that can not be seen. These areas are often referred to as "blind spots" and are located at the following sites:

(a) The lesser curvature of the antrum often remains hidden from view.

(b) A small portion of the posterior wall, if the light is less than $\frac{1}{2}$ cm. from the gastric mucosa. This is usually overcome by a slight turn of the instrument.

(c) The lesser curvature of the cardia.

Occasionally, there may be difficulty in visualizing some parts of the stomach because of improper position of the patient, anatomical variations or instrumentation.

CONTRAINDICATIONS

The indication for gastroscopy is suspected gastric pathology. However, not unlike most other procedures for medical study, there are contraindications to be considered. Since the flexible gastroscope is not a tube but a series of reflecting mirrors, it must be passed through the oesophagus without being able to look ahead through that channel. This is referred to as being passed "blindly." Hence, the following must be considered as contraindications for this procedure:

- (a) Corrosive and phlegmonous gastritis.
- (b) Distortion of the cervical and thoracic spine.
- (c) Aneurysm of the aorta.
- (d) Obstruction of the oesophagus.
 - (1) Scar constriction.
 - (2) Varices.

- (3) Neoplasm.
- (4) Diverticulae.
- (e) May be attempted with greatest caution in the presence of
 - (1) Angina pectoris.
 - (2) Dyspnea.
 - (3) Cardiospasm.
 - (4) Psychosis.

PREPARATION

The preparation of the patient is both psychological and medical. To avoid untoward effects and to properly carry out the examination the closest cooperation between patient and gastroscopist is essential. The patient takes a hypnotic (seconal gr. iii) the evening before. The following morning, without having taken any liquids or solids by mouth, the patient is given, sublingually, $1\frac{1}{2}$ grains of seconal powder. Shortly thereafter the lips, gums, tongue, mucosa of mouth and throat and finally the upper oesophagus are anaesthetized by topical applications of 2% Pontocaine. A well lubricated Levine tube is passed through the nose down into the stomach and the gastric residue is extracted, first in the sitting and then in the knee-chest position. The patient is then placed lying on the left side with the left elbow under the ribs and the forearm at a 90° angle. The left leg is extended but the right is slightly bent upward at the hip and knee. The head is held properly extended by a nurse especially trained for this technique. The preparation as well as the actual examination is carried out in a room dimly lighted by a colored bulb and in an atmosphere that inspires confidence. All unnecessary sounds are avoided but the patient is constantly reassured.

If all contraindications had been considered and the preparations carried out as just described, the passing of the lighted, slightly lubricated gastroscope is relatively simple. Under no conditions must the instrument be forced. It is wiser not to complete an examination than to force it. The stomach is inflated with air by means of the attached bulb and its interior studied.

OBSERVATIONS

Bearing in mind that the patient is lying on his left side and the views observed are spoken of as in clock-wise numbers, twelve o'clock would correspond to the patient's right side, three to his dorsal surface, six to his left side and nine to his antral surface. Since the stomach is a fairly movable organ and remembering that its lower pole turns towards the anterior abdominal wall and its greater curvature does not descend vertically, it therefore does not necessarily follow that the views observed are the right, left, dorsal and antral surfaces of the stomach. The anterior wall is recognized by its mucosa tending to be smooth and at times presenting a fine network of folds. The posterior wall is recognized by its folds tending to run in parallel lines. The greater curvature presents coarser folds sometimes described as fork-like in pattern.

The stomach is anatomically divided into two cavities — the body or upper part and the antrum or that portion beyond the antral sphincter muscle. This muscle crosses the greater curvature along its path over the anterior and posterior walls. Just proximal to the antral sphincter muscle, the lesser curvature, while descending to enter the antrum, forms a semilunar appearing edge. This area, the first landmark for the gastroscopist, is referred to as the angulus and is the first depth or level examined. The walls, greater curvature and pylorus are inspected. Only a small portion of the lesser curvature between the pylorus and angulus can be brought into view. The remainder of the lesser curvature of the antrum is a "blind spot" for the gastroscopist, so that x-ray findings in this area must be relied upon. The second and third depths or levels are respectively the lower and upper halves of the body of the stomach. The various levels are inspected by rotating the gastroscope.

Not only the mucosal appearance but also the contractibility and extensibility of the stomach wall, antral sphincter muscle and pylorus are studied. Just prior to or during gastric roentgenoscopy, I never permit the patient to have any antispasmodics and feel justified in concluding, if pylorospasm is present, that "the longer the pylorospasm continues (five or more minutes) the greater the likelihood that it is not functional nor reflex but caused by a true pathological pyloric lesion — even if the lesion can not be observed on Roentgen study." Likewise, an existing gastric lesion may not have sufficiently affected the mucosa to be seen at time of gastroscopy but presents itself through the effects on the muscle functions. If contractibility and extensibility of the muscles are found to be impaired, the gastroscopist is placed on his guard and re-examination later will usually bear out his original suspicion of a pathological lesion that then can be seen involving the mucosa.

The mucosa may present scattered small hemorrhagic or pigment spots. These are not to be confused with serious pathological lesions. A study (2) led to the conclusions that, since they may occur in healthy individuals, these hemorrhagic spots probably have no clinical significance and their relationship to peptic ulcer is questionable.

Small mucosal or submucosal polyps may not visualize on x-ray study but can usually be seen on gastroscopy. These polyps may be the source of bleeding, if small ulceration develops. While the mucosal polyp protrudes into the lumen and is seen as a pedunculated tumor, the submucosal polyp is recognized by a smooth elevation of the mucosa with a stretched-like appearance of the surrounding mucosal folds — "bridging folds" (3). These are usually asymptomatic but bear watching lest they ulcerate, become larger and pedunculate or malignant changes develop.

Small gastric ulcers are often missed on x-ray study either because they are too shallow to visualize or because of overlying mucosal folds. The clinician may suspect but the roentgenologist may properly report that

no ulcer was seen. Gastroscopy can usually clarify the situation. Marginal small submucosal hemorrhages surround the acute ulcer, which is frequently multiple. They are probably the result of food deficiency (4). Recently I have seen two acute ulcers, in a case of advanced gastric carcinoma, involving the surrounding mucosa. X-ray study revealed only the carcinoma.

The subacute ulcer is somewhat deeper with a muddy yellowish floor. The surrounding mucosa is almost normal in appearance. In contrast, the mucosa about the chronic ulcer takes on the appearance of gastritis. The benign chronic ulcer has a definite line of demarcation with sharp over-hanging edges and a white to yellow floor. The malignant ulcer is raised above the mucosal level. Its base tends to be from brown to almost black in color and the margins are irregular so that the immediate surrounding mucosa appears infiltrated. Errors in interpretation can be made, but if frequently repeated gastroscopy does not show healing, it is best to consider the ulcer malignant. It is difficult, if not impossible, roentgenologically to differentiate between benign and malignant gastric ulceration. One hardly need say that surgery is indicated at once in all malignant ulcers.

Following gastroenterostomy a marginal ulcer may be suspected because of persistent symptoms. Due to puckering of the surrounding mucosal folds, a distorted x-ray picture may be observed. Through the gastroscope either an existing peristomal gastritis and/or the suspected ulcer could be found.

A careful study of gastric ulcers (5) using clinical, gastroscopic, and roentgenological evidence has brought out the following important points: "(a) an acute ulcer may appear and disappear quickly; (b) an ulcer may increase in size; (c) after complete healing has taken place an ulcer may recur in approximately the same location or in an adjacent area; (d) symptoms may be entirely absent; (e) mucosal changes may vary from a perfectly normal mucosa to superficial, atrophic, or hypertrophic gastritis with or without hemorrhages or pigment spots; (f) the rate of healing varies greatly in different cases; (g) adequate nutrition, acid neutralization, and avoidance of concurrent infection are important in promoting healing; (h) cases exhibiting delayed healing are often accompanied by interference with gastric emptying and usually with narrowing of the antrum."

Gastric carcinoma of various forms present distinct and usually gross unmistakable pictures. A pathologist had previously taken me to task for this statement. He rightly brought out the point that the microscopic picture is often not clear cut and the gross could certainly give a mistaken picture. However, usually the gross picture is as unmistakable as, let us say, the gross picture of malignancy at time of laparotomy.

The nodular mass or masses on the wall with gastric mucosa infiltration is quite characteristic. The local mucosa is not a normal orange-red but appears white to gray in color and is edematous. Any ulceration of the

carcinoma will present irregular margins extending into the mucosa. Contractibility and extensibility is impaired. In very early carcinoma, where the mucosal changes are not sufficiently marked, this impaired function may be the only factor gastroscopically to invite the attention to carcinoma.

Very frequently patients will, for long periods, complain of gastrointestinal symptoms that do not seem to complete a picture of any one disease entity. A positive diagnosis is difficult to establish unless a complete gastrointestinal search is made. The patient may not appear to be sufficiently sick to warrant this search and the tendency is then to label him as "neurotic." It must be borne in mind that a "neurotic" may also be sick and a sick person has a good reason for being nervous. McNeer and Barowsky (6) reported that of sixty-two cases with epigastric symptoms, clinical and x-ray study did not reveal the cause. These were labeled as "functional dyspeptics." However, on gastroscopy, 46.8% were found to have definite gastric disease of which twenty-one patients had chronic gastritis. More and more similar reports are made by other observers.

That chronic gastritis is a distinct disease entity was regarded with skepticism by many. Due to the rapid autolysis of gastric tissue, pathological confirmation of this disease at autopsy is difficult although not impossible. That it does exist is established beyond doubt by gastroscopy. Chronic gastritis is usually classified into three main divisions, namely; superficial, hypertrophic and atrophic.

Superficial gastritis presents a mucosa that is injected with rugae that are studded with a viscid mucus. Pin-point submucous hemorrhagic spots and occasional superficial erosions may be observed.

Chronic atrophic gastritis is recognized by the smooth, thin and very pale mucosa. Through the thinned mucosa might be seen some narrow irregular thread-like vessels.

Benedict (7) has shown that gastritis is a very important cause of gastric bleeding. The superficial and hypertrophic variety can certainly bleed and be the cause even of massive hemorrhage. Gastroscopy should be carried out in these cases and may explain the "idiopathic" gastric hemorrhage.

The diagnosis of atrophic gastritis is of particular importance in suspected pernicious anemia. It does not necessarily follow that atrophic gastritis is only associated with pernicious anemia. Superficial gastritis frequently precedes the atrophic variety and if not diagnosed and treated may lead to chronic atrophy (1). The superficial variety seems to be caused by indiscretion in eating habits — such as excessive, irritating bulk and extremes in the food temperatures. Infected material draining from the upper respiratory tract and local gastric lesions could also produce superficial gastritis.

Chronic hypertrophic gastritis presents rugae that are thickened and tortuous even when the stomach is fully

inflated with air. The mucosa appears dusky-red. A hob-nail or "cobblestone" (1) appearance of hypertrophic gastritis is seen at times. These are variable in size and at times may become nodular. On occasions hypertrophic gastritis can give an x-ray picture resembling carcinoma (8).

Roentgenologically it becomes difficult, if not impossible, to conclusively diagnose chronic gastritis. Because of the non-specific symptomatology and difficulty on x-ray study in reaching a diagnosis of chronic gastritis it is reasonable to conclude that direct inspection with the gastroscope is the best and the only conclusive method of making this diagnosis (9).

Occasionally, a known existing duodenal ulcer may have healed but upper gastrointestinal symptoms persist. Not infrequently, in these cases, the gastroscopist will observe an existing chronic gastritis that will account for those symptoms.

If the previously mentioned contraindications are not present, no gastric surgery should be done in any questionable case unless preceded by a gastroscopic study. I re-emphasize — chronic gastritis per se may give a chain of symptoms resembling many gastrointestinal diseases but per se it is definitely not a surgical condition.

CONCLUSION

Gastroscopy has paved the route for more accurate information from the stomach. The direct visualization of tumors, ulcers and inflammatory reactions are but a start. Indeed, this instrument may serve for gastric study as the ophthalmoscope serves for eye study. Gastric mucosal reactions to drugs, foods, systemic diseases and emotional shock are already being studied through the gastroscope.

There is no doubt that the medical profession at large should avail itself more often of the information that the gastroscopist can ascertain for it. I frequently heard that gastroscopy is objected to because:

1. "There are blind-spots." — Even the pathologist will occasionally refuse to commit himself when he has the tissue under the microscope. All branches of medical study still have "blind spots."

2. "There are contraindications." — That must be conceded; but it is just as important to know when not to carry out a procedure as it is when to do it. Only fools dash in where angels fear to tread.

3. "There is discomfort and danger." — Both are minimized in the hands of a trained gastroscopist who will always observe the contraindications. Accidents with the flexible gastroscope are probably no more frequent than those with the cystoscope when used by a urologist.

Finally, let it be said that, while we are acquainted with the enthusiasm of the novice and the skepticism of the uninitiated, in the middle of their roads lies the path of the scientist and progress.

1. Schindler, R.: Gastroscopy (The Endoscopic Study of Gastric Pathology): Chicago, Ill.; University of Chicago Press.

2. Ruffin, J. M. and Brown, Jr., I. W.: The Significance of Hemorrhagic or Pigment Spots as Observed by Gastroscopy. *Am. J. Dig. Dis.*, 10:60-63, Feb. 1943.

3. Schindler, R., Sandweiss, D. J. and Mintz, I. L.: Benign Submucosal Tumors of Stomach: A Gastroscopic Study. *Am. J. Dig. Dis.*, 9:289-292, Sept. 1942.

4. Levin, A. L. and Shushan, M.: Gastroscopy as a Diagnostic Procedure (A Clinical Study with Illustrative Cases). *Rev. of Gastroenterology*, 8:103-112, March-April 1941.

5. Palmer, W. L., Schindler, R. and Templeton, F. E.: The Development and Healing of Gastric Ulcer — A Clinical, Gastroscopic, and Roentgenologic Study. *Am. J. Dig. Dis.*, 5:501-522, Oct. 1938.

6. McNeer, G. and Barowsky, H.: A Gastroscopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions. *Am. J. Dig. Dis.*, 6:180-182, May 1939.

7. Benedict, E. B.: Hemorrhage from Gastritis — A Gastroscopic Study. *Am. J. Dig. Dis. & Nutr.*, 4:657-664, Dec. 1937.

8. Pollard, H. M. and Cooper, R. R.: Hypertrophic Gastritis Simulating Gastric Carcinoma. *Gastroenterology*, 4:453-465, June 1945.

9. Renshaw, R. J. F.: Correlation of Roentgenologic and Gastroscopic Examinations from the Standpoint of the Gastroenterologist. *Am. J. Roentgen. Rad. Ther.*, 51:585-592, May 1944.

Observations on Percussion of the Liver in Acute Infectious Hepatitis*

By
JOSEPH I. GOODMAN, MAJOR, M.C., U.S.A.
CLEVELAND, OHIO

THE FOLLOWING OBSERVATIONS deal with a group of soldiers suffering from acute infectious (epidemic) hepatitis admitted to a United States Army General Hospital in the United Kingdom in the period from October, 1944 to May, 1945.

Inasmuch as the liver is fundamentally affected in this disease, the evaluation of its status is of considerable importance. Although the existence of an enlarged, swollen liver in acute infectious hepatitis is generally accepted, yet it is obvious that most authors in a significant percentage of their cases have been unable to confirm this finding by palpation of the liver (TABLE I).

TABLE I

Authors	No. of Livers Palpable
Cameron (1)	57 per cent
Havens (2)	58.5 per cent
Turner et al. (3)	39 per cent
Benjamin and Hoyt (4)	20 per cent
Bercovitz and Knoch (5)	40 per cent
Goodman (percussion)	77 per cent

Examination of the liver is equally important in the more chronic states. Palpation has proved equally inefficient in this group. In a noteworthy analysis Ratnoff and Patek (6) compared the weight of the liver in cases of Laennec's cirrhosis seen at autopsy with its palpability in the living patient (TABLE II). They

TABLE II (6)

Weight of the liver in 108 cases of Laennec's cirrhosis		
Wt. in Grams	No. of Livers Palpable	No. with Liver Not Palpable
200- 999	8	6
1000-1399	18	13
1400-1799	17	7
1800-2199	15	2
2200-2599	11	0
2600-2999	3	2
3000-3799	3	0
3800-4599	2	0
4600-5400	1	0
Total	78	30

state that the average weight of 78 palpable livers which showed cirrhosis was 1820 grams, the weights

ranging from 695 to 5100 grams. On the other hand, 30 non-palpable livers with cirrhosis weighed an average of 1370 grams, ranging from 580 to 2920 grams. It is surprising to note that 8 of 14 livers weighing only 200-999 grams were palpable. On the other hand, 2 of 5 livers weighing 2600-2999 grams (almost twice the normal weight) were not palpable. Ratnoff and Patek cite Eppinger's series in which the size of the liver of patients with cirrhosis appeared enlarged to palpation in 80 per cent of the cases. Only 50 per cent of the cases, however, were enlarged on pathologic examination. These data demonstrate that the palpability of the liver cannot be accepted as an estimate of its actual size.

Because of the inadequacy of palpation attention was focused to a greater degree on percussion of the liver boundaries. After we used percussion predominantly in the manner to be described below, its superiority as a method of examination of the liver soon became manifest.

The procedure followed in our cases was as follows: The upper and lower borders of the liver are delineated by indirect percussion in the mid-clavicular (mammary) line with the patient in the supine position. A stroke of moderate intensity percussing from above downwards is used. The distance between the two points marked out by percussion by actual measurement in centimeters is taken to represent the size of the liver.

As in the case of all intrathoracic organs one who employs percussion of the liver has to take into account the existence of relative and absolute dullness. In percussing from above downwards the percussion note gradually becomes dull over that portion of the liver which is covered by pulmonary tissues. This is generally known as the *area of relative (hepatic) dullness* (7). Upon continuing the percussion downwards a point is reached where the dullness is replaced by flatness, so called *absolute dullness*, representing that portion of the liver which is in direct contact with the abdominal wall. In approaching the lower limit of the organ this area of hepatic flatness is gradually replaced by intestinal

*From the 156th General Hospital, 2010 E. 102nd Street.
Submitted February 16, 1946.

tympany. It has been found more advantageous to locate the upper border by percussing from above downwards. In outlining the lower border we prefer to employ percussion from below upwards. In marking out the borders of the liver one is obliged to percuss meticulously and make several trials. Dexterity in this respect is readily acquired (Laporte 8). In hepatitis we record the size of the liver every other day and in some instances daily.

The importance of percussion in the physical examination of the liver is especially significant when the liver is not situated in its usual position. Therefore, to differentiate a downward displacement from an increase in volume of the liver, percussion of the superior border must be employed (7). To this group can be added those cases in which displacement results from upward pressure on the liver by ascites, tympanites, or increased abdominal tension due to tumor of an abdominal organ or ovarian cyst. The presence of intrathoracic tension seen in fibroid retraction of the right lung or as a result of paralysis or eventration of the diaphragm produces similar displacement. Pullen (9) also emphasizes that an increase in the size of the liver is certain only when the upper border can be located by percussion at the normal level and the lower border is palpable below the ribs. Interestingly we found that there is a wide latitude in the position of the liver in the normal individual in whom none of the above mentioned factors are present. Also we have often been able to demonstrate that even an enlarged liver may not be reached by the palpating finger.

Size of the Liver by Percussion. — As a control the size of the liver in 35 individuals was determined by percussion of its upper and lower borders. The majority of them had recently recovered from acute infectious hepatitis. The remaining control readings were recorded on patients who had recuperated from an illness other than hepatitis. The measurements in these individuals ranged from 6.25 cm. to 9.35 cm.

The measurements of enlarged livers on 31 patients with acute infectious hepatitis were taken throughout the course of their illness. The liver size exceeded 10 cm. in 24 of 31 patients (77 per cent). In one patient the liver was greatly enlarged and measured 21.9 cm. at one stage; it receded to the normal limits, 7.5 cm. within two weeks. Four of the 7 patients in whom no liver enlargement was detected on admission to the hospital, were examined for the first time between the 60th and 62nd day of their illness. Two others were first examined on the 27th day of their illness and one on the 36th day. Since the average period of hospitalization in a much larger series of similar cases followed by us (10) amounted to 31 days, it seems fair to assume that the livers of these 7 patients might well have been found to be enlarged to percussion had they been available for examination in the earlier stages of the disease. Nevertheless it can be seen that (TABLE I) despite this fact 77 per cent of the patients admitted

with hepatitis were found to have an enlargement of the liver.

Prior to our use of percussion the various criteria ordinarily applied in following the course of a patient with hepatitis were frequently found wanting. Of the various liver function tests that are at present in general use few, if any, are of prognostic value unless repeated frequently throughout the course of the disease in order to obtain comparative determinations. Admittedly, histologic data of liver changes would prove to be conclusive were it available to the clinician. However, liver biopsy appears to be too hazardous a procedure to employ in a disease such as acute infectious hepatitis where recovery is the rule. Still the disease is not so benign that any knowledge of its progress or regress would not be of value to the physician. It can be demonstrated with day to day measurements that the steady diminution of the liver size to a normal baseline, i.e., 6.25-9.35 cm. appears to reproduce faithfully the expected recession of the enlarged, swollen liver of acute infectious hepatitis. Thus the knowledge of the liver size obtained by percussion can prove to be a valuable guide throughout the entire course of the illness.

It is interesting to find that Zuelzer (11), beset with the same difficulties in regard to the physical examination of the liver and spleen while studying malaria during World War I, reached the conclusion that percussion rather than palpation was the method of choice. It was his opinion that one could not reasonably expect to palpate a soft, swollen type of liver.

Zuelzer in searching the literature up to that time cites that only one author, Frerichs, also pointed out that the data pertaining to the size of the liver obtained by palpation was largely untrustworthy compared to those of percussion. Using heavy percussion in the mammillary line, Frerichs reported that the area of relative dullness averaged 9.5 cm. in 200 normal individuals 20-40 years of age. Zuelzer utilized a light degree of percussion (Schwellenwertperkussion) by means of which only the area of absolute dullness of the liver is delimited. This area averaged 4.5 to 5 cm. in 1500-2000 normal individuals examined. We found the average size of the normal liver, determined by percussion of moderate intensity, to be 7.5 cm.

In Zuelzer's cases of acute liver swelling in malaria, typhus fever and scarlet fever the area of absolute dullness increased from 6 cm. to 11 cm. and in some to 13 cm. With a somewhat heavier percussion stroke the measurements of the enlarged liver in our cases of acute hepatitis varied from 10 cm. to 21.9 cm.

COMMENT

In our experience palpation of the liver proved to be rather a hit and miss method although it has come into almost exclusive use. It can be shown with percussion that a liver edge found 1 or 2 cm. below the costal margin may prove to be a normal size liver in a lower position. Yet in cases accepted as latent hepatitis by

Altschule and Gilligan (12) and others, this finding was considered *prima-facie* evidence of an enlarged liver even though such enlargement was frequently unsubstantiated by other criteria such as an elevation in the plasma bilirubin, etc.

Most of the liver function tests that have been utilized to date require adequate laboratory facilities of the type usually available only in the larger hospitals and teaching centers. This provides additional ground for using percussion in evaluating the size of the liver in hepatitis. Percussion should prove to be equally useful in all types of liver disease.

Despite the above mentioned drawbacks the textbooks of physical diagnosis promulgate palpation and discourage the use of percussion with the result that the use of the latter has fallen into disrepute. The interference of a tympanitic intestine and emphysematous lungs are most often cited but in our opinion they have been over-

emphasized. The use of percussion in our patients with acute infectious hepatitis was not hampered by any of these factors.

The measurement of the dimensions of the liver not possible by percussion when used in conjunction with careful palpation of the lower edge, possesses a degree of exactness heretofore absent in the physical examination of the liver. The frequency of liver enlargement observed in our series (77 per cent) stands in contrast to the repeated failures of contemporary authors to corroborate by palpation the pathologic enlargement of the liver known to be present in acute infectious hepatitis (TABLE I).

We believe that the observations recorded herein warrant the consideration we have attached to percussion of the liver size as being a procedure of clinical and prognostic import.

REFERENCES

1. Cameron, J. D. Sr.: Infective Hepatitis. *Quart. J. Med.*, 12:139, 1943.
2. Havent, W. P., Jr.: Infectious Hepatitis in the Middle East. A Clinical Review of 200 Cases seen in a Military Hospital. *J. A. M. A.*, 126:117, 1944.
3. Turner, R. H., Snavely, J. R., Grossman, F. B., Buchanan, R. N. and Foster, S. O.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers after Inoculation with Yellow Fever Vaccine: with Especial Consideration of Severe Attacks. *Ann. Int. Med.*, 20:193, 1944.
4. Benjamin, J. F. and Hoyt, R. C.: Disability Following Post-vaccinal (yellow fever) Hepatitis (A study of 200 patients manifesting delayed convalescence). *J. A. M. A.*, 123:119, 1943.
5. Bercovitz, Z. T. and Knoch, H. R.: Infective Hepatitis. II. Clinical Study of Patients not Related to Yellow Fever Vaccination or Infectious Jaundice (Weill's Disease). *J. A. M. A.*, 126:117, 1944.
6. Ketchell, O. D. and Patch, A. L., Jr.: The Natural History of Typhoid Carcinoma of the Liver (An Analysis of 116 Cases). *Medicine*, 21:267, 1942.
7. Hesse and Rose: *Physical Diagnosis*, 3rd. ed., St. Louis, 1930, C. V. Mosby Company, p. 353-362.
8. Laporte, G. L.: A New Method of More Accurately Determining the Upper Border of the Liver by Means of Percussion. *Med. Record*, 93:1126, 1914.
9. Pullen, R. L.: *Medical Diagnosis*. Philadelphia and London, W. B. Saunders Company, 1944, p. 509-510.
10. To be published.
11. Zuelzer, G.: *Klinische über Malaria*. (Die Lebererkrankung). *Deutsch. med. Wochenschr.*, 43:1502, 1917.
12. Altschule, M. D. and Gilligan, D. R.: Chronic Latent Hepatitis Following Catarrhal Jaundice. *New England J. of Med.*, 231:315, 1944.

Idiopathic and Psychogenic Incontinencia Recti

By

A. JUDA, M.D.

JERUSALEM, PALESTINE

OF THE SEVERAL TYPES of incontinence of the rectum, by far the rarest type is what I call "idiopathic incontinence of the rectum." No statements whatsoever could be found in the literature regarding this type of disease (1-6, and many others). The surgical and proctological textbooks almost exclusively deal with those forms of incontinence only, which are a consequence of an injury or an operation or, more seldom, of a purulent inflammation, by which the external sphincter gets involved in dense fibrous tissue (Lockhart-Mummery 7). When there is no mechanical cause for incontinence — says Lockhart-Mummery — that is to say when examination shows that the muscle is intact and properly contracting, we must conclude there is a functional cause from derangement of the nerve-supply. This functional incontinence is only known as a

partial symptom of a nervous disease: a paraplegia, disseminated sclerosis, and more particularly tabes dorsalis. Known, but scarcely cited in the special literature are cases of incontinence occurring with spina bifida. This is a childhood disease, which manifests itself at the latest during puberty. In addition to all these forms there are, however, cases, which I call idiopathic incontinence of the rectum, and in which the incontinence, mostly complete, more seldom incomplete, i.e. only for gases and appearing periodically, forms the only symptom of the disease. The sphincter muscle is intact, its tonus is at times decreased, and there is no abnormality at all in the nervous system.

To start with, here is the story of my cases:

Case 1. Mrs. Cl. C., 58 years of age, widow, three healthy children, has suffered since the age of 28, i.e. for about 30 years, from incontinencia recti. It is noteworthy to state from her family history that both her parents

died at the age of 74 or 76, respectively, from carcinoma recti. The mother, who had three normal deliveries, is said to have suffered from incontinentia recti after the third delivery. It cannot be established how long after the delivery the incontinence started, probably much later.

The patient herself has suffered from incontinence of the rectum for 30 years. The onset of the disease was after the first delivery. She does not remember exactly, how long after. It is sure that, during the first fortnight after the delivery in childhood she had no such disturbances. In the beginning she passed now and again for some days small quantities of stool without perceiving it. Then often for months she was free from this disorder. In the course of time the intervals became shorter and the fits of the disease longer. After having suffered from this disease for about twenty years she underwent an operation: small hemorrhoids were removed and something done at the sphincter. What, she does not know. Thereafter, there was an improvement for a short time. But the good condition did not last longer than an interval before the operation. Therefore, three weeks later, a second small operation was performed, which had no influence whatever on her disease. It remained this way until now: short good intervals alternated with longer periods of illness, during which she is not able to keep back the stool. As soon as she feels the necessity, she has to reach the W. C. as quickly as possible. In addition she passes smaller quantities of feces, which she does not feel at all. Otherwise she feels well and works hard. She carries heavy parcels and has to climb many flights of stairs.

The objective examination reveals a slightly pale woman in a good nutritional state. The abdominal wall is a little atonic. The sigmoidum inclined to spasms at examinations during the first weeks of treatment. At this time the patient complained of short fits of pains in the belly. Otherwise, all organs are normal. A thorough neurologic survey was made by the neurologist Dr. A. Stern and myself; no abnormality was found. The perineum is in a good state, not at all lacerated (as Buie (p. 160) writes that in many cases incontinence will be found associated with the lacerated perineal bodies of old multiparous women). The sphincter ani is intact but mostly not well contracted. The examining finger and the proctoscope glide through without encountering any resistance. The mucous membrane of the rectum is smooth and atrophic in the under parts and normal up to 25 cm. During short intervals of time the tone of the sphincter seems to be somewhat better.

All possible types of therapy were employed: electrotherapy in every possible form, injections of chinin-urea (injections sclerosantes) above the sphincter, etc., but all without achieving improvement.

Case 2. Dr. Br., 47 years of age, married, two healthy children, teacher at a secondary school. His parents are healthy. A brother died at the age of 50 from carcinoma (he does not know details). The patient himself suffered as a child from measles, pneumonia and an acute nephritis. He has been for 24 years in Palestine, has always been healthy except a dysentery 11 years ago, which healed quickly and was, therefore, most probably bacillary. Since his childhood a small prolapse appears externally with the stool and goes back immediately. His digestion is generally normal. The feces empty out in the morning not in one session, but in several, one shortly after the other. For about 10 years there have been periods of some weeks when he passes in the course of the day gases and mucus and mostly also stool in small quantities. All this only enters his mind when it is already too late. The free intervals became shorter not long ago. The prolapse is as small as it was more than 30 years ago.

The examination of the patient shows a normal condition of health. All reflexes are in good order; no sensory

disturbances. Pressure of the blood is low: 75/100. The sphincter recti is intact, its tone is very weak at the time of the examination. At the anus there are small external hemorrhoids. The mucous membrane of the rectum is normal for 20 cms. upwards. The patient has tried, without success, electrotherapy and various medicaments and declines any further treatment.

Case 3. Mrs. A., 56 years of age, married, two healthy children. She comes from a healthy family. As a child she has had measles and whooping cough. 21 years ago, when on a visit to Palestine, she suffered from dysentery for four weeks. Amebas and bacilli could not be found. After this disease was healed completely, she had an icterus, which disappeared again after some weeks and never returned. She has been suffering from constipation for many years. 12 years ago, after an inflammation of the throat, she had blood in the stool for a short time. The doctor's diagnosis confirmed hemorrhoids. Two years later she observed that, with the stools a "ball" came out of the anus, which returned by itself. In the same year the uterus was removed owing to heavy hemorrhages. The above mentioned prolapsus ani had appeared already before the operation and was not worse thereafter. She has had now for five years spontaneous losses of stool, which she does not feel, even if there was in the morning a sufficient movement of the bowels. For a time she used big enemas of water. These emptied out the bowels so thoroughly that there were no more spontaneous losses of stool, but they did not benefit her. She used again laxatives, which caused again incontinence of the rectum. If and when she succeeded for a time in establishing normal bowel function by diet, there were often intervals without incontinence of some weeks. Then there were again weeks when she found daily her underlinen soiled by stool without having observed the motion of the bowels in time, or without being able to prevent it. The "ball" comes out with each movement, but goes back immediately thereafter and has not grown since its first appearance.

The general examination does not reveal any abnormality. Her looks are according to her age. Her nutritional state is good. All reflexes are in order, and there are no sensory disturbances. The sphincter recti is intact. weak. Finger and proctoscope penetrate with only slight resistance. The mucous membrane of the rectum looks smooth, slightly atrophic, does not show anything abnormal up to 20 cms. height. After 5 injections of Chinine-Urea, the prolapse is much improved, for the last 8 weeks the patient had no more incontinence while the movement of bowels was regulated by a proper diet.

Case 4. A case in the beginning stage of idiopathic incontinence. K. H., clerk, 50 years of age. A brother of his mother died of Ca of the intestines, the mother herself at the age of 38 of perforation of a gastric ulcer. He himself had gas-poisoning during the first world war, para-typhoid in 1935. 17 years ago hemorrhages from hemorrhoids began, which grew worse and worse in the course of time, so that he had to be operated on two years later. For 14 days now he has had traces of blood in the stool. 9 months ago he had diarrhoea which lasted for three weeks. During this time he often passed stool without knowing it. Since his movement is normal again he has not had any more symptoms of incontinence.

A general examination does not show any pathological symptoms. Reflexes and sensibility are normal. The mucous membrane in the lower quarter of the rectum is smooth, atrophic and completely without visible veins. Higher up the mucous membrane is normal up to 25 cm. The linea pectinea is formed quite irregularly. When spreading wide the anus a small eversion falls forward, on the right side of which there is a small sessile polyp. The sphincter is intact, but its tone is very weak so that the finger and the sigmoidoscope penetrate without resistance.

The patient did not consent to have the small polyp destroyed.

These cases of incontinence of the rectum differ from all those stated in the literature by their etiology as well as by their symptomatology. The other forms occur in consequence of a damage of the sphincter or of paralysis of the sphincter, which is part of a nervous disease, i.e. there is a *tabes dorsalis*, multiple sclerosis, etc. In the above cases the sphincter is not damaged, and no signs of a nervous disease can be found. In cases 2 and 3 there is a prolapse, which is small, however, and which existed for many years without ever requiring replacement manually. Incontinence is uncommon in this form of prolapse. It is more often found in those forms Bacon (1. c. p. 411) calls "proci-dentia" which he defines as the abnormal descent of all the coats of the rectum with or without protrusion through the anal orifice. It is larger in diameter and extends to a greater length than prolapse. In our cases such procidentia is out of the question.

The only objective symptom to be found is a weakness of the sphincter tone. While the other forms of the incontinence appear without intervals, the idiopathic incontinence appears periodically — with long intervals. In the course of time these become shorter and shorter, and the duration of the periods longer. Even case 1, which has lasted already for thirty years, is not entirely without intervals. An improvement of the general condition of the patient has, in my opinion, no influence on the disease. For case 2 suffered last year, immediately after a three weeks' rest in the hills, from an attack of some weeks' duration. While the patients 2 and 3 did not observe any influence by psychic occurrences on the incontinence, patient 1 believes that great agitation exerts an influence. The connection is, in my opinion, an indirect one, for she is suffering from nervous diarrhoea owing to agitation, and if and when she is suffering from diarrhoea also not of a nervous nature, incontinence occurs. Unfortunately I could not obtain, for exterior reasons, a roentgen photograph of the lower parts of the spine of my patients. In spite of that a *spina bifida occulta* can be excluded, for an incontinence owing to *spina bifida* usually occurs in earliest childhood, in rare cases immediately after puberty.

A connection between incontinence and a difficult delivery, of which one could think in case 1, can be excluded, for the patient knows definitely that in childbed, i.e. for 14 days after the delivery she did not observe any incontinence. Besides, an incontinence caused by a mechanical damage to the sphincter in the course of the delivery does not appear periodically but continuously without intervals, and the perineum is lacerated. Case 1 is, therefore, definitely a case of idiopathic incontinentia recti. As to case 4, I do not believe that the prolapsus and the weak tonus of the sphincter are a consequence of the operation. I never saw weakness of the sphincter and loss of control of the bowels after operations, which did not damage the sphincter. Besides, such a damage to the sphincter and also to its nerve supply can cer-

tainly be excluded, since, otherwise, the patient would not have remained without disturbances for 15 years. Prolapses of the mucous membrane I have sometimes observed after Whitehead operations, but they appear much earlier, at the latest after 1-2 years. In the literature the Whitehead method is often blamed for the fact that owing to the circular damages of the ends of the nerves, the closing capability of the sphincter muscles is incomplete during the first 12 days and sometimes longer, occasionally even for ever, while other authors (for instance Dzialoszynski) found continence in all cases after Whitehead. Anyway, an incontinence and eversion happening for the first time 15 years after the operation cannot be regarded any more as a consequence of the operation.

In my opinion, in those cases of idiopathic incontinence, hemorrhoids, prolapse and incontinence have the same etiology: the tone of the muscular system and of the connective tissue throughout the anal region is weak. Whether the underlying cause is to be found in the tissue itself or within the nerve supply, I cannot decide. It is, however, remarkable that, in most cases, a case of carcinoma of the intestines is found in the family story.

The paramount issue is, of course, to find a treatment to cure these patients who suffer very much from their disease. What I tried until now: electro-therapy, injections of strychnine, etc., remained without success. Injections of chinine-urea above the sphincter improved the prolapse and possibly in case 3 also the incontinence. Perhaps the only way for restoring continence is the operation, described by Vreden (*Arch. Surg.*, 18:841, 1929). The essential principle of Vreden's operation is to harness the two *glutaeus maximus* muscles by strings of fascia that pass around the anal canal in such a manner that, when the *glutaei* contract, these fascial strings will be drawn taut.

Another form of incontinence of the rectum, of which I have not found any mention in the literature, is the following:

Case 5. Miss N. H., 24 years of age, chemical assistant in a laboratory. In the history of her family do not appear special diseases, above all no nervous or psychic disturbances. She herself had scarlatina and measles as a child. She was a gifted pupil. After puberty she suffered for years from constipation. For some years her digestion has been normal. She has, however, now always slight pains at the anus. Since more than a year she passes gases without being able to prevent it and often even without her feeling it. She has great quantities of very bad smelling gases. She is afraid, because of her disease, of her work and of any company. For especially often when she is not alone, she is surrounded from time to time by a cloud of bad smelling gases, which others, of course, remark too. During the last three months she was very depressed owing to this condition, has had no appetite and lost 5 pounds of weight. At present she has taken a few weeks leave and recovers well because she can avoid nearly all company.

The patient has been examined and treated by several doctors. Some have hinted at the fear of a grave disease being the cause of her troubles. Thereby her condition has become still worse. Status: restless, slightly depres-

sive expression in the face. All reflexes are normal except the conjunctival and the gag reflex which could not be elicited. No disturbances of sensibility. The sphincter recti is well contracted. No changes can be found at the anus. A slight anitis can be seen in the sigmoidoscope, otherwise the mucous membrane is normal up to 25 cms. During almost each consultation the patient passes several times very bad smelling gases. All organs otherwise normal. All kinds of therapy tried were without success. Two years later the patient reports to me that she has been free from her disease since her wedding day a year ago.

From the beginning I was of the opinion that, according to the impressions received from the patient, this was a psychogenic case. A symptom in favour of this diagnosis was the state of the sphincter, which was *always* well contracted and the way the incontinence occurred, i.e. it was worst, if and when the patient dreaded it most: at her work in the laboratory in the presence of chiefs and colleagues and in company of

others. No importance is to be attributed to the fact that it was only a partial incontinence, i.e. only regarding gases. Such partial incontinence occurs from time to time with all forms of incontinence of the rectum. My diagnosis was confirmed by the way the disease was cured. A great happy psychic event, the marriage of the patient suddenly ends the disease, after it had existed for about two years. In such cases, the best success might generally be obtained by psycho-therapy.

The forms of incontinence described above are, in my opinion, not as unusual as one might suppose from their not being mentioned in the literature. It would be welcomed if proctologists in the U. S. A. who dispose of a very great number of cases, would turn their attention to idiopathic and psychogenic incontinence and publish their observations. It is to be hoped that they will then find a successful therapy.

REFERENCES

1. Buie, Louis A.: *Practical Proctology*. W. B. Saunders Company, Philadelphia and London, 1938.
2. Hirschmann, L. J.: *Synopsis of Anorectal Diseases*. St. Louis, 1942.
3. Bacon, Harry Elliott: *Anus, Rectum, Sigmoid, Colon*. Second Edition. J. B. Lippincott Company, Philadelphia, Montreal, London, 1941.
4. R. Bensaud: *Maladies de l'Intestin*. Vol. IV, Paris, 1939.
5. David, Vernon C.: *Surgery of the Rectum and Anus in Lewis' Practice of Surgery*. Vol. III, Chap. 6. Hagerstown, Md., 1944.
6. Borchard-Rotter: *Chirurgie des Mastdarms und des Afters in Garre, Kuertner, Lexer, Handbuch der Praktischen Chirurgie*. Abschn. XIII. Stuttgart 1929.
7. Lockart-Mummery: *Causes and Treatment of Rectal Incontinence*. *Lancet*, 2:535, Sept. 1933.

The Causes and Mechanisms of Abdominal Pain

By

PAUL JEFFREY SCHUTZ, M.D.*

SCOTT FIELD, ILLINOIS

THE PURPOSE of this paper is to discuss the causes and physiologic processes by which abdominal pain is produced, to summarize briefly the generally accepted principles which are of value, and to point out the important controversial issues, the solution of which will eventually lend great assistance to our techniques of bedside diagnosis. The mechanisms of abdominal pain are many and varied. Following a short summary of the pertinent anatomy, an attempt will be made to classify the various etiologic factors of abdominal pain and to describe the salient manifestations of each.

The abdominal wall (skin, muscle and peritoneum) are supplied by the cerebrospinal nerves, sixth thoracic to first lumbar. These nerves also supply the root of the mesentery and the lesser omentum. Other abdominal structures receiving cerebrospinal innervation are the diaphragm and its peritoneal covering, supplied by the third to fifth cervical and sixth to twelfth thoracic nerves, and the trigone of the urinary bladder which,

though not an abdominal organ, is included because of the pain it may give rise to in the abdomen. Abdominal structures innervated by sensory fibres traveling in autonomic nervous pathways are, the major portion of the gastro-intestinal tract (from the middle third of the esophagus to the anus), visceral peritoneum, liver, pancreas, spleen, gall bladder, kidneys, ureters, and most of the body of the urinary bladder. It is important to note that these "visceral sensory" fibres follow the same paths in the central nervous system as do the "somatic sensory" fibres. Thus they differ only in that they enter the central nervous system by way of the sympathetic nerves, ganglia, and gray rami, rather than by the dorsal root ganglia. This similarity is important in view of the fact that these fibres, histologically similar, with identical central tracts, transmit the two different types of abdominal pain associated with gastro-intestinal pathology: that arising from the visceral, and that arising from the abdominal parietes.

MECHANISMS PRODUCING ABDOMINAL PAIN

A. Abdominal Pain Arising From the Gastro-intestinal Tract, Peritoneum.

1. *True visceral pain* — The existence of true vis-

From the Michael Reese Hospital and the Department of Gastro-intestinal Research, **Research Institute of Michael Reese Hospital, Chicago, Illinois.

*Present address: Lt. Paul Schutz; ASN O-1754770, MC-AUS, 3505th Bu Squadron A-3, AAF Regional Hospital, Scott Field, Ill.

**Aided by a grant from A. B. Kuppenheimer Fund. The Department is in part supported by the Michael Reese Research Foundation. Submitted April 10, 1946.

ceral pain is now generally accepted by all authorities. As far as is known the only adequate stimulus for gut pain is distention, including that produced by edema. The normal bowel is insensitive to cutting, burning, crushing and touch (the renal pelvis and ureters are viscera which are sensitive to mechanical stimulus — touch — which has led Morley to postulate cerebro-spinal innervation to these organs). The stipulation that the bowel must be normal is made in view of the controversy over the source of pain arising from the peptic ulcer. Wolf and Wolff (1) have shown that with inflammation and edema, minor stimuli applied to the gastric mucosa cause pain. Palmer (2) maintains that the inflammatory reaction in the ulcer area lowers the pain threshold of nerves surrounding the ulcer so that chemical (HCl) or mechanical (touch, pressure, peristalsis) stimuli become adequate to cause pain. Jones (3) on the other hand, feels that the intramural edema in the ulcer wall produces enough increased pressure on nerve endings, and increased muscle tone, to duplicate the usual adequate stimulus, bowel distention. Morley (4) points out that, while the stomach arises in the midline, and is bilaterally innervated, ulcer pain may well be a localized, unilateral pain. From this he reasons that all painful ulcers evoke sensation by producing a localized irritation to the overlying parietal peritoneum. The improbability of such a mechanism being effective in all cases is obvious.

Meyer and his associates (5) believe that there are two factors in ulcer pain, one of which usually predominates in any given patient. Hydrochloric acid, the first factor, is definitely responsible in roughly half of the cases he analyzes. In these cases the pain is due to the irritating effect of the acid on the associated antral gastritis. The pain in the other cases is due to the other factor, gastric hunger contractions and motility, which deplete the vascular bed of the ulcer area, producing asphyxia, edema and pain. About all that can be said inconclusion is that the consensus of opinion favors the idea of ulcer pain being viscerogenic.

Irrespective of these arguments, the criteria of pain arising from the bowel are fairly clear cut. Such pain is typically deep seated and central, although poorly localized. If there is no paralysis of the bowel, the pain waxes and wanes with the peristaltic rushes of the gut, producing characteristic "cramps" which may cause the patient to writhe or double up, to press upon the abdomen in an attempt to relieve the discomfort.

II. *Visceral referred pain* — True visceral pain is not referred to the abdominal wall, and therefore is necessarily unassociated with superficial or deep tenderness, or muscular rigidity. It is localized only in this sense; that pain from the stomach and duodenum is epigastric, pain from the jejunum and ileum is periumbilical, while colon pain is generally appreciated as being hypogastric (6). These localizations are not always useful because the pathology may involve several bowel segments having different areas of pain referral, as in the gastroenteritides.

Lastly, visceral pain arising from the bowel does not radiate. Visceral pain arising from the heart or urinary tract *does* radiate, and hence the presence of pain radiation should raise serious question as to whether the pain being studied is actually arising from the gut.

The one possible exception is the pain of biliary tract disease which frequently radiates to the right infra-scapular area. It has been shown by several investigators (7-9) that by sectioning only the right splanchnic nerve, the pain of gall bladder and biliary duct distention can be eliminated, even though the intercostal nerves to this region (D7 to D10) are intact. Davis and Pollock (7) point out in this connection that, "although it may be demonstrated that the afferent painful impulses from the viscera are carried along with the autonomic nervous system, we have no proof that the impulses are actually carried over autonomic neurons" (that is, they may be carried by regular sensory neurons, similar to those in the periphery, traveling in the autonomic nervous system).

Still others (4, 10, 11) are convinced that this radiation is a somatic sensory effect, being constantly associated (in their opinion) with other signs of peritoneal irritation, as described below. The pain radiation is not seen, according to Morley, in a patient's first attack of biliary colic (before there is a pericholecystitis, which irritates the peritoneum), when the true visceral, boring, epigastric pain comes and goes in synchronous harmony with the hyperistalsis of the distended bile ducts. Judovich and Bates (12) feel that gall bladder pain radiation is of autonomic origin, and differentiate this and other viscerogenic referred pain (as from ureter or uterus) from somatic referred pain by the fact that spontaneous visceral referred pain is not associated with segmental skin tenderness, while somatic referred pain sets up areas of skin hyperalgesia. Whether or not this distinction can be verified, these writers have made an important contribution with regard to the subject of cutaneous hyperalgesia of the abdomen, by showing that *this* is a phenomenon which can be abolished by local skin anesthesia, and that the remaining deeper pain in the abdomen, due to peritoneal irritation, is not affected at all by cutaneous anesthesia. No conclusions can be drawn now as to whether gall bladder pain radiation is of visceral or of somatic origin. And lest we become too firmly enamored of either theory, it is pointed out that some workers (15) have been able to produce typical gall bladder colic by mechanically dilating the duodenum as well as the gall bladder, or the bile ducts. They suggest that pressure by an inflamed, swollen gall bladder on the duodenum may be the cause of the pain. Alvarez (11) points out that gall bladder colic may occur, "without gall stones, without a gall bladder, and without most of the common duct." Alvarez is, however, drawn to the conclusion that the radiation of gall bladder pain to the right back is due to irritation of the posterior parietal peritoneum.

III. *True somatic or parietal pain*, associated with

bowel diseases, arises from secondary involvement of the peritoneum covering the anterior abdominal wall and diaphragmatic dome, and less commonly from the root of the mesentery and lesser omentum. A certain element of somatic pain may be associated with visceral pain without peritoneal involvement, due to traction on the root of the mesentery by hyperactive, distended, or kinked loops of bowel. Such pain is poorly localized and of limited diagnostic value.

Somatic peritoneal pain is characteristically sharp, well localized and stabbing in quality. Once the focus of irritation is established on the peritoneum this pain is constant, and the patients tend to lie very still, rather than move about. Of prime importance, those portions of peritoneum which are innervated by nerves also supplying the skin and muscle of the anterior abdominal wall (this includes a part of the diaphragmatic peritoneum and excludes entirely the pelvic peritoneum) give rise to the phenomena of muscle rigidity, deep tenderness, and, inconstantly, to cutaneous hyperalgesia. These effects, which have been labeled as direct and referred sensation by different men, will now be considered, in connection with the theory that peritoneal pain is directly perceived as coming from the deeper layers of the abdominal wall.

According to Capps (16) the pain and tenderness arising from the anterior parietal peritoneum is directly perceived, whereas Morley (4) feels that it is referred quite accurately to the skin of the anterior body wall overlying the diseased area of serosa. It seems reasonable to believe that both of these theories are in part correct, perhaps supplementary. That is, *painful stimulation of the peritoneum is directly perceived, and also gives rise to certain reflex phenomena*. Let us make this analogy. Any given segment of skin and peritoneum, arising from a given body segment, are supplied by nerves which are anatomically and physiologically identical. Thus there is no reason to believe that the peritoneum cannot give rise to the same phenomena as the skin. Ergo, a touch upon the skin is directly perceived and accurately localized. Capps has shown that the same holds true for stimuli applied to the anterior parietal peritoneum. Trauma to the skin causes superficial tenderness, accurately localized in the skin, and peritoneal irritation gives rise to a deeper tenderness which, although occasionally misinterpreted as skin pain (cutaneous hyperalgesia) is usually appreciated as arising internally. A light stroke across the abdominal skin evokes reflex contraction of the abdominal musculature, *the superficial abdominal reflex*, which is protective in nature. In a similar fashion, irritation of the peritoneum produces an area of localized reflex muscle spasm. Indeed, the comparisons are so striking, that the writer would like to suggest that the muscle spasms associated with peritoneal irritation be designated the *deep abdominal reflex*, in order to further accentuate the similarities between skin and peritoneal sensation.

The only dissenting voices, other than Morley's, raised against the concept of the direct perception of

peritoneal pain, are those of Weiss and Davis (20), who also feel that such pain is perceived in the skin, and can be abolished by locally anesthetizing the skin. They go so far as to say, "visceral pain may be completely blocked if the corresponding painful skin impulses are blocked." They leave no doubt that they are referring to peritoneal pain by emphasizing that in patients suffering from "*distinctly localized* (italics are this author's) severe visceral pain" infiltration with novocain of the corresponding skin segments causes prompt relief of pain. They go on to say, "Paravertebral block gives identical results with local skin infiltration."

That is true only for cutaneous hyperalgesias, which these authors are confusing with peritoneal pain. Paravertebral block of posterior ganglia will eliminate pain from any and all sources in a given segment, including skin and peritoneum, because the entire nerve trunk is anesthetized. One may do a laparotomy under extensive paravertebral block. Cutaneous anesthesia, however, blocks only the cutaneous branches of a spinal nerve, and consequently eliminates only impulses from the skin. Hence the results obtained from these two types of anesthesia are not analogous.

It seems obvious that cutaneous anesthesia will terminate cutaneous hyperalgesia by numbing the sense organs in the skin. This anesthesia, however, in no way affects the sensory end organs of the peritoneum. This is borne out by recent work (13, 21) which demonstrated that cutaneous anesthesia does not abolish pain from areas of peritoneal irritation as seen in cholecystitis. So we may return to our original argument; that pain of peritoneal origin is directly perceived as is pain from the skin, and stimulation of either structure gives rise to reflex muscular contraction (v.s.). Anesthetizing either organ does not eliminate painful stimuli from the other.

Deep tenderness is not, in all probability, a referred phenomenon, but a direct sensation from the inflamed peritoneum. Lewis (17) thinks that the pain is directly perceived but suggests that it might be due to the reflex muscle spasm producing enough local tissue anoxia to cause direct tenderness in the muscle, a process exactly analogous to the intermittent claudication of Buerger's Disease. If this is true, a deep tenderness would occur uniformly over areas of muscle spasm, which are segmental and be mistaken for a reflex effect. Deep tenderness is usually well localized over the inflamed area of peritoneum.

Both Capps and Morley agree that referred pain follows the skin areas of spinal segmentation, but Morley goes further to state that such referred pain (as he believes peritoneal deep tenderness to be) is, in the case of the peritoneum, accurately localized. This is paradoxical. Any pain which has radiated over an entire spinal segment could hardly be accurately localized. Capps does not fall into this error but uses the term referred pain correctly, as in the case of the dome of the diaphragm, where pain sensation is actually referred

to the homologous skin segment of the spinal nerve involved.

We come now to the interesting phenomenon of cutaneous hyperalgesia. Recent contributions to the literature have helped clarify some of the confusion concerning the nature of this manifestation.

Cutaneous hyperalgesia refers to an increased sensitivity of a skin area to painful stimuli. Such increased skin sensitivity is entirely distinct from the deep tenderness associated with peritoneal irritation (13, 16). It is usually associated with spontaneous skin pain in the same area, and it is this duo of symptoms which has been termed *segmental neuralgia* (14). When spontaneous segmental skin pain appears alone, the probability is that it is a true visceral referred pain (12). When the segmental pain and hyperalgesia occur together, there are two possible sources.

The first source is irritation of a nerve root and/or a nerve trunk. Segmental neuralgia on this basis may thus occur as an acute toxic radiculitis following upper respiratory disease, or herpes zoster, or it may occur as a manifestation of chronic pressure on the nerve roots and trunks due to poor body posture, lordosis, scoliosis, trauma, or neoplasm. The fact that the correction of the above-mentioned precipitating factors, or block of the involved nerves, will abolish the segmental pain and hyperalgesia, establishes the validity of this mechanism.

A second cause of segmental neuralgia is causalgia. Just how the two are related is still largely a matter of conjecture, but some recent investigations have been suggestive (18, 23-25). Following nerve injury, as by crushing, changes occur in electrical polarity in the damaged nerve fibres which produce spontaneous impulses traveling to the periphery and also centrally. The latter are recognized as pain. Simple stimuli acting on the skin area innervated by the damaged nerve, produce exaggerated pain response, because they result in increased discharge of impulses at the point of injury. This much of the causalgic syndrome is exactly analogous to the segmental neuralgia caused by irritation of nerve roots or trunks.

The phenomenon of phantom limb is merely a manifestation of causalgia following amputation, and has the same mechanism of origin as causalgia following injury. The patient complains that he can still feel the missing extremity, especially the hand or foot. The sensation may in time become maddeningly painful, and these people may be mislabeled as psychoneurotics. This condition is usually associated with a neuroma of the end of one of the main nerve trunks severed by the amputation. This neuroma consists of the bare proliferating ends of the axons and masses of Schwann cells embedded in scar tissue. White discusses the problem of pain after amputation, and states that the bare, unmyelinated nerve endings in the neuroma tend to respond in an exaggerated manner when effectively stimulated, being more sensitive than normal. Also, the contracture of scar tissue in the neuroma produces

anoxic anoxia in this area, and anoxic nerve fibres likewise tend to give off repetitive impulses. He quotes other sources supporting this view (49, 50). Like causalgia, phantom limb pain responds early to procaine block of the neuroma, later to sympathetic block of sympathectomy when the level of self-perpetuating stimuli has arisen to the second sensory neuron (i.e. in the spinal cord), and eventually only to ablation of the sensory area of the cerebral cortex.

In addition to the segmental neuralgia, there are the objective skin changes of redness and increased temperature. De Takats explains all the phenomena of the causalgic state as follows: Antidromic impulses along sensory fibres, from the site of the nerve injury, produce capillary vasodilatation, which is evidenced by increased warmth and redness of the skin. Centripetal impulses from the same site excite the sympathetic nervous elements in the same cord segment, with resultant "tonic" discharge of the sympathetic neurons. The combination of arteriolar constriction caused by sympathetic excitation, and capillary dilatation caused by antidromic stimuli, produces a capillary hypertension, local stasis and tissue damage, and the release of an "H" substance (18, 19, 23) (metabolites, histamine, acetylcholine?) which produces the burning pain. Warmth, redness, and burning pain constitute causalgia.

Assuredly the theory presented is as yet lacking adequate confirmation. De Takats himself says, "All that can be said with assurance is that the causalgic type of vasodilatation is different from the one produced by heat, vasodilators, or sympathetic block. It combines an increased pulse volume with an increased peripheral resistance, and sympathetic block abolishes this incoordination of vasomotor impulses" (25). The available clinical data tend to favor this hypothesis. Cutaneous local anesthesia will affect cure in early causalgia by blocking afferent impulses from the skin, which act as part of the trigger mechanism. Infiltrating the skin or the nerve trunk between the injury and periphery, or paravertebral block, are equally effective, because these measures prevent antidromic impulses from reaching the skin, and showers of ascending impulses from entering the cord where they would excite the sympathetic nervous system. Local nerve blocks are not effective in advanced causalgia, where the sympathetic excitation has already become established and self-perpetuating. Advanced causalgia cannot be affected by paravertebral block, but can be, and is, affected by sympathetic block or sympathectomy. These latter measures do not break up the vicious circle of stimuli which produce the causalgic state, but are thought to be effective by relieving the arteriolar constriction, improving the circulation, and consequently washing away the irritating "H" substance more efficiently.

What then, of cutaneous hyperalgesia of the abdomen, associated with abdominal pain? It seems reasonable to think that cutaneous hyperalgesia is a mild form of causalgia, an early, reversible stage as it were, where the predisposing factors (peritoneal irritation), and the

precipitating factors (continuous discharge of stimuli from the focus of irritation), are present; but the continuative factors (chronicity of irritating stimuli, damage to the nerve, etc.) are not present. Just how the two syndromes are related is not clear. With cutaneous hyperalgesia, there is no accompanying redness and warmth of the skin, no edema or glossiness so characteristic of causalgia. Does this indicate an absence of antidromic impulses, which have a known ability to produce redness, warmth, edema, and even vesiculation, in the skin? Possibly, it does. If so, the main responsibility for cutaneous hyperalgesia may rest upon a reflex arc in which the sensory nerve fibre from the peritoneum is the afferent limb and the sympathetic nervous system is the efferent limb.

The existence of such a reflex arc capable of producing cutaneous hyperalgesia has already been definitely established by Davis and Pollock (7). They have conclusively shown that the shoulder pain produced by stimulating the central area of the diaphragmatic peritoneum (essentially an hyperalgesia) can only be stopped by cutting the 8th cervical, 1st, 2nd, 3rd and 4th thoracic anterior nerve roots, or by extirpating both cervical sympathetic chains. Consequently they concluded that, "Painful impulses from the diaphragm travel over the phrenic nerves into the spinal cord . . . and descend, probably by short pathways, to the level of the second thoracic segment. At that level a synapse with the cells of the anterolateral column occurs, and the impulses pass out through the cervical eighth, and thoracic, first, second, third, and fourth anterior roots to the cervical sympathetic chain. Over efferent fibres the impulses are carried to the skin and other structures . . . Some physiologic process then occurs, the nature of which is unknown. From the periphery, the impulses then travel over ordinary spinal sensory nerves into the spinal cord . . . to the cortex, where hyperalgesia in the shoulder area is appreciated."

One recent investigation further demonstrates the close relationship of the somatic sensory and sympathetic nervous responses. Findley and Patzer (22) have shown that blocking the appropriate sympathetic ganglia will completely relieve the pain of herpes zoster. Here is an inflammatory process of the somatic sensory dorsal root ganglia, which produces sufficient antidromic stimulation to cause hyperalgesia, redness and vesiculation in the periphery. And the pain is promptly relieved by sympathetic block! Findley and Patzer feel that vasospasm is the important factor in producing pain. ". . . the cells in the corresponding intermediolateral cell column are receiving an excessive number of normally directed impulses from the irritated ganglion, a circumstance which results in increased sympathetic vasoconstrictor tone and segmental articular spasm . . . one must assume that the post injection hyperemia, however, transient, relieves pain by dilution of retained metabolites . . ."

From this mass of evidence, certain conclusions are drawn. There is a subtle, intimate relationship between

the somatic sensory nervous system, and the sympathetic division of the autonomic nervous system. When stimuli arise in the somatic sensory nervous system at an abnormally rapid rate, the corresponding segment of the sympathetic system are reflexly excited, and certain phenomena appear peripherally in the homologous segments which are the product of both acting factors. The milder manifestations are spontaneous skin pain and hyperalgesia. The more severe ones are redness, heat, edema, and vesiculation. The various etiologic factors producing the initial increase in stimuli in the sensory limb of the reflex differ only quantitatively, not qualitatively, as far as their end results are concerned. Peritoneal irritation (peritonitis), herpes zoster, nerve injury, and abnormal pressure of nerve root or trunk, are some of the conditions which may initiate this reflex.

IV. *Diaphragmatic pain*, a variant of true somatic pain. Fortunately, the direct and referred elements of pain which can be differentiated only with difficulty, are more readily distinguishable in the study of pain sensation arising from the diaphragmatic peritoneum. Here, the direct, accurately localized perception of pain has been lost, and only the referred elements of sensation, segmental rigidity, hyperalgesia, and skin pain remain.

Stimulating the entire diaphragmatic dome with the exception of the peripheral three inches consistently produces a pain along the upper border of the trapezius (a point of maximum tenderness, surrounded by a zone of cutaneous hyperalgesia), but no pain is experienced as arising in the diaphragm itself. Stimulating the periphery of the diaphragm produces a poorly localized pain over the lower thorax posteriorly (again no pain perceived as arising from the diaphragm), spreading over the flank to the lateral and anterior aspects of both thorax and abdomen. Maximal tenderness is usually located over the costal margin. This is recognized as referred pain because it is poorly localized, is associated with both cutaneous hyperalgesia and muscle rigidity (of the diaphragm, lower intercostal and upper abdominal muscles), and is segmentally distributed on the anterior abdominal wall. It is the possibility of this referred pain occurring in association with diaphragmatic pleurisy as well as with peritonitis, that has led to the aphorism, "The differential diagnosis of the acute abdomen must include lower lobe pneumonia."

The dome of the diaphragm is innervated by the phrenic (3rd to 5th cervicals) nerve, not by the intercostal (6th to 12th thoracic) nerves, which jointly innervate the peripheral three inches of diaphragm as well as the anterior parietal peritoneum. One may ask, in the light of what has been hypothesized for the localization of pain from the anterior parietal peritoneum, why pain from the diaphragmatic dome is not appreciated as arising from the diaphragm, if it has the same type of innervation as the anterior abdominal wall? Several factors are involved.

To begin with, the muscle mass of the diaphragm which originated in the fourth cervical somite, has mi-

grated to become a deeply buried organ, now subject to mechanical stimuli of only lethal intensity. Thus the diaphragmatic peritoneum is more closely related functionally to the visceral, than to the parietal peritoneum, in that it is more subject to inflammatory than to mechanical trauma, and accurate localization of stimuli no longer serves any useful purpose. All that is necessary is a mechanism for preventing the spread of infection, and this is accomplished by the reflex muscle spasm of the diaphragm and upper abdominal musculature, which the diaphragmatic peritoneum is still capable of initiating.

One might thus postulate that the pathways of direct pain sensation from the diaphragmatic peritoneum have undergone a phylogenetic atrophy of disuse, losing their cortical representation. This is the conclusion reached by Capps, and which Morley might accept, since he proposes a similar mechanism to explain the loss of visceral pain in the lung, where the cough reflex has superseded pain as the main protective mechanism. Whether or not one accepts the validity of this teleologic explanation, the fact remains, that pain impulses coming up the phrenic nerve are *not* transmitted directly to the brain, but are rerouted down the cord and into the cervical sympathetic chain, from whence they reach the brain only secondarily, from a site in the skin area of the fourth cervical segment (7).

The limited area to which referred sensation from the central diaphragm is confined (usually along the ridge of the neck produced by the superior border of the trapezius), may be explained in this wise. Whereas each segment of peritoneum and an area of overlying skin of approximately the same size, are innervated by a separate nerve, the entire muscle mass of the diaphragm, derived from a single myotome which has grown, expanded, and migrated a great distance from its homologous dermatome (which has itself greatly decreased in relative area in the course of evolution), this entire muscle mass is innervated by a single nerve. The cutaneous area supplied by this nerve is so small, and so distant from the muscle and its serosal coverings, that the referred elements of sensation are of necessity distant from the source of stimulation, and confined to a small area. The brain may have forgotten the embryologic relationships of myotome and dermatome, but the nerves which supply these structures have not.

The periphery of the diaphragm differs in being innervated by the lower six intercostal nerves. Embryologically, this portion of the diaphragm is derived from the abdominal wall (the primitive somatopleure), being spilt away from it, as it were, and incorporated into the downward-migrating fourth cervical myotome, by the edge of the growing lung mass. Thus one would expect this peritoneal area to respond more like the anterior parietal peritoneum than like the area innervated by the phrenic nerve. This is not the case. Mechanical stimulation of this area produces no accurately localized sensation, but only a referred pain, segmentally dis-

tributed over the thoracic and abdominal wall, with cutaneous hyperalgesia and muscle spasm (of the diaphragm and the lower intercostals and upper abdominal muscles). It is apparent that the peripheral diaphragm gives rise to the same type of pain sensation as the central portion, and although there is no experimental evidence as yet to confirm the surmise, it seems reasonable to assume that the mechanism of pain transmission is probably identical in both cases.

Now we are faced by an apparent paradox in the function of the lower six intercostal nerves, some sensory fibres of which give rise to both direct pain perception and the usual referred phenomena (those supplying the anterior parietal peritoneum), and others which give rise to only the referred manifestations (those supplying the peripheral diaphragmatic peritoneum). This may not be as paradoxical as it seems. Since a single nerve can carry all modalities of sensation, the idea of a nerve carrying subtypes of a given modality is not too radical. The explanation lies within the realm of physiology, and is probably concerned with changes which have occurred in the central nervous system "receiving terminals" for pain from various areas. As was suggested before, the entire diaphragmatic peritoneum has probably lost its pain representation in the somesthetic area of the cerebral cortex, and consequently the cortex registers only the hyperalgesia of the homologous skin somites, which is mediated by the sympathetic nervous system. The reflex rigidity of the lower intercostal and upper abdominal musculature following stimulation of the peripheral diaphragm also has a sound anatomic basis. Both of these muscle masses, thoraco-abdominal wall and peripheral diaphragm, originate from the same myotomes, and their nerve fibres synapse with skin neurons in identical segments of the cord. Thus no matter which "limiting membrane" of the abdominal wall is stimulated, skin or peritoneum, the muscles of the sixth to twelfth thoraco-abdominal segments will respond with reflex spasm, whether the muscle has remained in the abdominal wall proper, or has migrated to the periphery of the diaphragm. Clinically we see this in diaphragmatic pleurisy, and sub-diaphragmatic abscess, where both the diaphragm and upper abdominal wall, as well as the lower intercostals, are rigidly splinted.

In conclusion, the fundamental similarity between pain from the diaphragm and from the abdominal wall should be pointed out. *They differ only in the loss of direct pain perception from the diaphragm.* Irritation of both areas of peritoneum produces the same reflex phenomena and, in the case of hyperalgesia, it is even possible to demonstrate an anatomic, as well as a theoretic proof of the part played by the sympathetic nervous system.

With the above principles in mind, one can readily interpret the majority of common pain syndromes associated with bowel disease; the primary colicky, periumbilical pain of appendicitis due to inflammatory dis-

tention and hyperperistalsis, and the secondary constant, sharp, localized pain associated with tenderness and rigidity due to local peritonitis; the hypogastric cramps of obstructed rectosigmoid carcinoma; the epigastric colic seen with duodenal spasm or stricture in peptic ulcer; the primary epigastric distress of biliary colic, due to hyperperistalsis or distension of the biliary tract, the secondary subcostal pain and radiation due to peritonitis, etc.

B. Abdominal Pain Arising From the Urinary Tract.

With reference to the urinary tract few definite statements can be made, since the routes of transmission of stimuli, be they cerebrospinal or autonomic, are not known. Campbell's recent paper (46) adequately summarizes the various urologic conditions which cause abdominal pain in children. Many of these causes are valid for adults also. "The chief potential causes of urologic abdominal pain are the obstructive lesions of the urinary tract; . . . hydronephrosis, ureteral stricture, ureteral obstruction by aberrant vascular compression, and obstructions at the bladder outlet or in the deep urethra are of highest incidence."

The following generalizations may be made with regard to the distribution of urologic pain. Kidney pain may be felt in front of the loin, just below and external to the junction of the linea semicircularis and the costal margin, as well as posteriorly in the angle between the twelfth rib and the outer border of the erector spinae muscles. The pain of renal colic begins in the above described area and may radiate to the inguinal canal and the testis or labia. The bladder may give rise to a true visceral pain, due to distention which is felt in the mid-line suprapubic region. Bladder stones, tumors, and inflammation may produce a true somatic pain by stimulating the trigone, which is sharp, well localized, and radiates characteristically to the tip of the penis or clitoris. The testes, which originated embryologically in close association with the kidney (mesonephros), give rise to a dull sickening pain which radiates in the reverse direction to kidney pain, sometimes rising as high as the lumbar area, where renal pain begins.

C. Abdominal Pain Arising from the Solid Organs of the Abdomen.

The capsules of the liver, spleen, and kidneys undoubtedly contain sensory fibres; these respond to distention of the organ, by passive congestion or inflammation, as is clinically manifested by tenderness. There is little, if any, spontaneous pain. Heaviness or dragging sensations are probably due to pulling on the mesenteries.

ORGANIC DISEASE OTHER THAN IN THE ABDOMEN, PRODUCING ABDOMINAL PAIN

A. *Acute Infections.* In acute infectious diseases, especially during childhood, abdominal pain is often one of the initial symptoms. It is seen with the acute exanthemata, upper respiratory infections, meningitis,

poliomyelitis, influenza, and other infections. Its basis is probably either an associated autonomic imbalance or a mesenteric lymphadenitis which often accompanies acute infection in children (48).

B. Neurogenic Disorders.

I. *Central nervous system syphilis.* The severe abdominal pain of neurogenic origin, associated with pernicious nausea and vomiting, is classically illustrated in the tabetic gastric crisis. The mechanism of this disturbance is uncertain, but it has been attributed to vagal storms in some cases, and to sympathetic dysrhythmia in others. It is interesting to note that tabes can disrupt nervous pathways so as to produce a visceral analgesia which "is capable of masking serious abdominal affections, owing to the absence of both pain and rigidity" (26).

II. *Other causes.* Abdominal pain may accompany many types of brain disease; tumors, and other expanding or invading lesions, convulsive states (the epigastric aura), migraine associated with cerebral vasospasm, encephalitis, and experimental conditions (27). Cushing (28) has shown that pituitary extract injected into the cerebral ventricles will produce hypermotility of the stomach, pylorospasm, and reverse peristalsis. Other workers (29) have produced local bowel spasm by stimulating the cerebral cortex.

Wechsler concludes that the source of neurogenic abdominal pain is the cerebral cortex, probably the premotor area of the frontal lobe. He adds that the hypothalamus and possibly the vagal nuclei may also be responsible for abdominal pain, and that they may be the mediators of the cortical response.

Confirmatory evidence is found in the work of Watts and Fulton (30), who produced intussusception in monkeys by creating lesions in the premotor cortex or in the hypothalamus. The telescoping of the bowel was preceded by hypermotility.

The cerebral cortex may contribute to the diagnostic difficulties in some cases of abdominal pain actually due to gastrointestinal disease, by inducing areas of muscle spasticity which are only secondary protective reflexes, but which surround and obscure an area of primary reflex muscle spasm, overlying a focus of peritoneal irritation. It has been shown that the judicious use of intravenous morphine will eliminate pain and this secondary spasm of cortical origin, leaving only the primary, spinal reflex spasm. Thus localization of the lesion, and accurate diagnosis is facilitated (32, 33).

C. Cardiac Disease.

True cardiac pain is apparently due to anoxia, the local coronary vessel spasm secondarily induced, and the accumulation of metabolites in the infarcted area. This pain is heightened by the reflexly increased tonus of the intercostal musculature (44), which produces the characteristic sensation of constriction of the chest. This occurs by way of the intercostal nerves which also supply the anterior abdominal wall, and may be so marked as to cause splinting to the epigastric musculature, and abdominal pain.

METABOLIC DISTURBANCE PRODUCING ABDOMINAL PAIN

A. *Acidosis*. The association of abdominal pain with acidosis is not uncommon in diabetes. That the pain is not due to the acidosis per se, is shown by the fact that it disappears when intravenous saline is administered, even though the acidosis is still uncontrolled (34). Walker thinks that the mechanism is similar to that producing heat cramps and the so-called gastric tetany of pyloric stenosis; that is, due to the excessive loss of salt from the extracellular tissues. In the case of diabetic acidosis, the salt loss is due to the polyuria and, later to the onset of vomiting. In the resulting state of hypochloremia, the exercising of the muscles of the abdomen and of respiration (Kussmaul breathing) produces local changes in the muscles (areas of spasm?) which cause them to give rise to pain. That pain may be produced in any muscle violently exercised in this unphysiologic state is evidenced by the diffuse muscle cramps seen in heat cramps.

B. *Hypoglycemia*. Both acute and chronic depressions of the blood glucose level will produce gastrointestinal symptoms, including abdominal pain. This interesting manifestation is discussed in detail by Sandler (39), who presents a series of cases in which abdominal pain was the major symptom, and chronic hypoglycemia the only evidence of disturbed physiology.

Ordinary hunger sensation is a direct function of the hypoglycemia which gradually follows alimentary hyperglycemia. The low blood sugar level acting on the brain stem produces increasingly powerful hunger contractions by way of the vagus nerves. Should the blood sugar continue to fall to even lower levels, as under conditions of starvation, the sensation of hunger is diminished or lost. This physiologic mechanism has been duplicated by experimental injections of insulin.

Recent investigation (36-39) has uncovered a group of patients whose primary pathology is a disturbance of carbohydrate metabolism manifesting itself through chronic hypoglycemia and increased glucose tolerance. These people may display abdominal pain, either generalized, or localized in the epigastrium, upper right quadrant (with radiation to the right back), both lower quadrants, or the center. "Apparently in a given patient, the hypoglycemia has a tendency to stimulate the same group of neurons in the vagal nucleus, and the particular segment of the gastrointestinal tract (including the biliary tract) innervated by these neurons, undergoes strong contraction, which may go on to tetany" (39).

A probable mechanism of this metabolic disturbance has been suggested by the work of Soskin (41). He showed that giving intravenous glucose will suppress liver glycogenolysis, and decrease the liver output of sugar until the blood sugar level returns to normal. This inhibitory effect on the liver may be so great that the blood glucose will fall to hypoglycemic levels before the liver again begins to discharge sugar into the blood.

Thus it is assumed that patients with chronic hypoglycemia have been living on a high carbohydrate diet which stimulates glycogenesis and inhibits glycogenolysis in the liver, eventually resulting in hypoglycemia. The validity of this theory is demonstrated by the fact that these patients are relieved of their symptoms, including the abdominal pain, by a low carbohydrate, high protein, and high fat diet; coincidentally, their blood sugar gradually rises and the glucose tolerance falls to the limits of average normals.

C. *Hyperthyroidism*. Uncontrolled thyrotoxicosis may produce either a diffuse, colicky abdominal pain, or, more commonly, one which is localized and constant and usually in the right lower quadrant (42, 43). There may even be some slight muscle spasm and tenderness.

D. *Lead Poisoning*. According to Goodman and Gilman (45), lead colic pain is paroxysmal and excruciating. The abdominal muscles become rigid and there may be tenderness. The colic is due to the intense spasm of the intestinal musculature, but how the lead produces this spasm is not known. It probably acts directly on the smooth muscle fibres. The spasm may be relieved by atropine, nitrites, or papaverine.

E. *Metabolites and Vascular Disease*. The role of the breakdown products of metabolism in the production of pain is not well understood. Some investigators (11) feel that the accumulation of such irritant substances in the tissues is capable of producing pain. This mechanism is related to, and usually accompanies, vascular disease or spasm, which is the cause of the accumulation of such wastes in the tissues. The classic example, with reference to abdominal pain, would be spontaneous mesenteric thrombosis and intermittent abdominal "claudication." In connection with this particular cause of abdominal pain, the reader's attention is re-directed to early paragraphs concerning the pain producing qualities of "H" substances liberated in irritated and damaged tissue, and the sympathetic hyperactivity they elicit.

SUMMARY AND CONCLUSIONS

The various theories and controversial issues concerning the mechanisms of abdominal pain have been reviewed, primarily to emphasize some of the fundamental precepts which have been established, and secondarily to accentuate (a) the many possibilities which must be considered clinically when confronted with this symptom, and (b) the intricate problems which still await solution. The following conclusions have been drawn:

1. True visceral pain is deep-seated, central, and poorly localized. It may be colicky. There are no referred phenomena, according to the views of some authors.
2. True somatic pain is sharp, constant, stabbing, and gives rise to referred manifestations; muscle spasm, and hyperalgesia.
3. Deep tenderness is directly perceived as arising from

the deeper tissues of the abdominal wall (i. e. from the peritoneum).

4. Muscle spasm is a reflex elicited in an identical manner from both skin and peritoneum.
5. Cutaneous hyperalgesia is closely related to the phenomenon of causalgia. It is suggested that these and certain other conditions which cause an abnormal increase in afferent stimuli, are mediated by a reflex arc involving the sympathetic division of the autonomic nervous system.
6. Abdominal peritoneal inflammation produces both lo-

calized deep tenderness and segmental cutaneous hyperalgesia. The latter can usually be abolished by skin anesthesia, but never the former.

7. The diaphragmatic peritoneum has lost its pathways for direct pain perception, but the same reflex manifestations as arise from the anterior parietal peritoneum, originate from this source.
8. Other organic and metabolic sources of abdominal pain, aside from the gastrointestinal tract, are enumerated and discussed.

REFERENCES

1. Wolf, S. and Wolff, H. G.: Pain. Res. Publ. Ass. Nerv. Ment. Dis., vol. xxii, Williams and Wilkins Co., 1943, pp. 289-300.
2. Palmer, W.: Ibid, pp. 302-326.
3. Jones, C.: Ibid., pp. 274-288.
4. Morley, J.: Abdominal Pain. E. and S. Livingstone, Edinburgh, 1931.
5. Meyer, J., Fetter, D. and Strauss, A.: The Relation of the Pain of Peptic Ulcer to Gastric Motility and Acidity. Arch. Int. Med., 50:338, 1932.
6. Jones, C.: Digestive Tract Pain. Macmillan, New York, 1938.
7. Davis, L. and Pollock, L.: The Role of the Autonomic Nervous System in the Production of Pain. J. A. M. A., 106:350, 1936.
8. Davis, L., Hart, J. T. and Crain, R. C.: Pathway of Visceral Afferent Impulses within the Spinal Cord; Experimental Dilatation of the Biliary Ducts. Surg., Gyn. and Obst., 48:647, 1929.
9. Schragar, V. L. and Ivy, A. C.: Symptoms Produced by Distention of the Gall Bladder Ducts. Surg., Gyn. and Obst., 47:1, 1928.
10. Alvarez, W. C.: Abdominal Pain; Paths over which it Travels and Ways in which These may be Blocked. Am. J. Surg., 14:385, 1931.
11. Alvarez, W. C.: Abdominal Pain: The Sensitive Regions in the Abdomen and ways in which they may be Stimulated to Produce Pain. J. A. M. A., 102:1351, 1934.
12. Judovich, B. and Bars, W.: Segmental Neuralgia in Painful Syndromes. F. A. Davis, Philadelphia, 1944, pp. 123.
13. Ibid., p. 4.
14. Ibid., pp. 1, 5.
15. Bloomfield and Pollard: Experimental Referred Pain from the Gastrointestinal Tract. J. Clin. Invest., 10:453, 1931.
16. Capps, J. and Coleman, A.: An Experimental and Clinical Study of Pain in the Pleura, Pericardium, and Peritoneum. Macmillan, New York, 1932.
17. Lewis, T.: Pain. Macmillan, New York, 1942, p. 158.
18. Ibid., pp. 91-93.
19. Lewis, T.: The Nocifensor System of Nerves and Its Reactions. Brit. Med. J., 1:431 and 491, 1937.
20. Weiss, S. and Davis, D.: The Significance of the Afferent Impulses from the Skin in the Mechanism of Visceral Pain. Skin Infiltration as a Useful Therapeutic Measure. Am. J. Med. Sci., 176:517, 1928.
21. Discussion by Doctors J. C. White, H. Wolff and J. Capps: Pain. Res. Publ. Ass. Nerv. Ment. Dis., vol. xxii, Williams and Wilkins, Baltimore, 1943, pp. 268, 270.
22. Findley, T. and Patzer, R.: The Treatment of Herpes Zoster by Paravertebral Procaine Block. J. A. M. A., 128:1217, 1945.
23. de Takats, G.: The Nature of Painful Vasodilatation in Causalgic States. Arch. Neurol. and Psych., 50:318, 1943.
24. Ibid., Posttraumatic Dystrophy of the Extremities. Arch. Surg., 46:469, 1944.
25. Ibid., Causalgic States in Peace and War. J. A. M. A., 128:699, 1945.
26. Wilson and Bruce: Neurology. Williams and Wilkins, Baltimore, 1940, p. 500.
27. Wechsler, I. S.: Abdominal Pain as a Symptom of Disease of the Brain. J. A. M. A., 105:647, 1935.
28. Cushing, H.: Pituitary Body, Hypothalamus, and Parasympathetic Nervous System. Charles C. Thomas, Springfield, Ill., 1932.
29. Bochefontaine: Arch. de Physiol. Norm. et Path., 3:140, 1876.
30. Watts, J. W. and Fulton, J. F.: The Effect of Lesions of the Hypothalamus upon the Gastrointestinal Tract and Heart in Monkeys. Ann. Surg., 101:363, 1935.
31. Watts, J. W.: Influence of the Cerebral Cortex on Gastrointestinal Movements. J. A. M. A., 104:355, 1935.
32. Pressman, D. and Schotz, S.: A Critical Analysis of the Intravenous Use of Morphine. Anesth., 4:53, 1943.
33. Singer, H. A.: Morphine as an Aid in Diagnosing Acute Abdominal Affections. Am. J. Surg., 34:5, 1936.
34. Walker, H.: The Etiology of Abdominal Pain in Diabetic Acidosis. Ann. Int. Med., 9:1178, 1936.
35. McKittrick, L. S.: Abdominal Symptoms with or without Abdominal Lesions in Diabetic Acidosis. New Eng. J. Med., 209: 1033, 1933.
36. Harris and Scale: Gastrointestinal Manifestations of Hyperinsulinism. Am. J. Dig. Dis., 2:557, 1935.
37. Goldzieher, M. A.: Chronic Hypoglycemia. Endocrinol., 20:86, 1936.
38. Tedstrom, M. K.: Hypoglycemia and Hyperinsulinism. Ann. Int. Med., 7:1013, 1934.
39. Sandler, B. P.: Chronic Abdominal Pain due to Hypoglycemia. Surg., 9:331, 1941.
40. Quigley, J. P., Johnson, V. and Solomon, E. I.: The Action of Insulin on the Motility of the Gastrointestinal Tract. Am. J. Physiol., 90:89, 1929.
41. Soskin, S., Essex, H. E., Herrick, J. F. and Mann, F. C.: The Mechanism of Regulation of the Blood Sugar by the Liver. Am. J. Physiol., 124:558, 1938.
42. Robertson, W. E., et al: Hyperthyroidism Masked by Symptoms of Acute Abdominal Catastrophe. J. A. M. A., 108:623, 1937.
43. Wohl, M. G.: Masked Hyperthyroidism. M. Clin. of N. Amer., 16:134, 1932.
44. Wiggers, C. J.: Functional Consequences of Coronary Occlusion. Ann. Int. Med., 23:158, 1945.
45. Goodman and Gilman: The Pharmacological Basis of Therapeutics. Macmillan, New York, 1941, p. 727.
46. Campbell, M. E.: Abdominal Pain Due to Urologic Disease in Children. J. A. M. A., 128:326, 1945.
47. Strauss, A. A.: Abdominal Pain in Children from a Surgical Standpoint. J. A. M. A., 128:330, 1945.
48. Brennemann, J.: Abdominal Pain in Children. J. A. M. A., 127:691, 1945.
49. Ratner, B.: Abdominal Pain in Children Due to Allergy. J. A. M. A., 127:696, 1945.

Book Reviews

The Modern Treatment of Diabetes Mellitus Including Practical Procedures and Precautionary Measures. By William S. Collens, B.S., M.D. and Louis C. Boas, A.B., M.D. Springfield, Illinois, Charles C. Thomas, 1946.

Today it is not an easy task to write a book on the treatment of diabetes as there is so much about the etiology, pathology, treatment and complications that is controversial. The authors make that admission in the chapter on the Juvenile Diabetic when they say — "That there exists today no uniformity in the treatment of the Juvenile Diabetic." This statement may be applied to almost every other phase of diabetes, and diabetic coma. Certainly no unanimity of opinion exists, and yet good results are obtained by many. Consequently, the material in this comprehensive and well written book represents chiefly the authors' clinical experience, and whether or not others in the field would accept the view points is truly a matter of doubt. That does not seem to be the authors' concern, they merely go on presenting their work, and, no doubt if one follows the text closely he will treat a diabetic satisfactorily. This is the book's objective. However, the goal of any text is not so much the treatment of the disorder but the optimum treatment in the broadest sense of the word. Here the book does not render the best service, because some of the diet and insulin instructions are a bit complicated, formal and difficult to apply. Also, the authors make statements of opinion and belief with equal emphasis as they do facts, thus misleading the physician as to what is definitely known and what is conjectural.

In the chapter on Diagnosis there is an unfortunate

typographical error which states that the peak of the glucose tolerance curve should be no higher than 108 mg. per cent, and in all probability the authors meant that the blood sugar should not rise above 180 mg. per cent.

In general the book contains a good deal of excellent factual material, much of which cannot be found in standard text books on diabetes. The chapter on Avitaminosis, Vascular Diseases and Technique, are excellent, and the book will be found useful by those who accept the authors' ideas, for after all the physician's main aim is treating a diabetic satisfactorily; and with some application and study he can learn how to do that from the instructions given.

Peptic Ulcer. By I. W. Held, M.D., F.A.C.P., and A. Allen Goldbloom, M.D., F.A.C.P., pp. 382 (\$6.50). Springfield, Illinois, Charles C. Thomas, 1946.

This book portrays not only the *Diagnosis and Treatment of ulcer*, but furthermore it includes the etiology and pathology of the condition. The Bibliography is to be commended for its scope and real historical value. The chapters are well arranged, clearly written and the illustrations are excellent. The treatment consists of a modification of the Sippy method with indications for surgical intervention. Every Gastro-Enterologist appears to have his own modification, rarely any two alike.

The book should prove to be of great interest to the specialist in this field, and is recommended to the student of medicine, as well as to the general practitioner.

— H. W. Soper, M.D.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

* With the Armed Forces.

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DEVENPORT
E. R. FLAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
*F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

ALWALL, N.: *Hereditary nonhemolytic bilirubinemia.* (*Acta Med. Scand.*, v. 123, p. 560, 1946).

The subjects had an icterus without evidence of hemolytic anemia, biliary obstruction or abnormal liver biopsy specimens. The van den Bergh reaction was delayed direct and the urine bilirubinogen test was often positive. This type of bilirubinemia is probably heredit-

itary and non-hemolytic and is more common than hitherto believed.

BANTELS, C. D. AND MANICUS-HANSEN, E.: *Ten years of serum therapy in appendicitis.* (*Acta Chirurg. Scand.*, v. 92, p. 1, 1945).

From 1921 to 1930 operations for acute appendicitis

numbered 490 cases with 48 deaths while from 1931 to 1940 there were 902 operations with 28 deaths. Peritonitis occurred to the same number in both groups. Whereas the latter operated group received serum therapy, the earlier group did not. The serum was anti-gas gangrene and anti-coli and was given both prophylactically and after the operation.

BJORKMAN, G., NORDEN, A. AND UVNAS, B.: *Histamine and pepsin secretion.* (*Acta Physiol. Scand.*, v. 6, p. 108, 1943).

Histamine does not stimulate the secretion of pepsin from the cat's gastric glands. The secretion of pepsin in response to vagus stimulation by electrodes is not inhibited by histamine.

BRUGSCH, J. T.: *Acute porphyria.* (*Med. Klin.*, v. 39, p. 523, 1942).

Acute porphyria may show abdominal symptoms as well as neurologic disturbances. Associated leukocytosis makes diagnosis difficult. Intense dark brown appearance of urine when boiled with 25 per cent hydrochloric acid indicates porphyria. All treatments which tend to disturb porphyrin metabolism are therefore contraindicated.

BRULL, L.: *The minimal nitrogen requirement in a chronically undernourished individual.* (*Arch. Internat. Physiol.*, v. 53, p. 12, 1943).

The subject was a man who during the 18 months prior to study subsisted on a diet of 1200 calories daily and had lost 47 pounds in weight. His nitrogen stores were depleted. By giving diets containing various amounts of nitrogen and of different caloric values, it was determined that the endogenous nitrogen metabolism was not influenced by the nitrogen intake once prolonged poor nutrition has resulted in exhaustion of nitrogen stores.

CHAUCARD, B., CHAUCARD, P. AND MAZONE, H.: *Visceral excitability during B avitaminosis.* (*Compt. Rend. Soc. Biol.*, v. 138, p. 407, 1944).

Avitaminosis B₁ in the rat for a while induces a shortening of the time required for nervous excitation of the viscera; later the time of excitation is lengthened. In the normal rat similar decrease in visceral excitation time can be obtained by inducing alkalosis or hypoglycemia while increase in excitation time can result from acidosis or hyperglycemia. A relationship is suggested.

DIMTER, ADOLF: *Studies on the unsaponifiable fat of ovarian dermoid cysts.* (*Zeitsch. Physiol. Chem.*, v. 270, p. 247, 1941).

Cholesterol, which is structurally related to the bile

acids and the sex hormones, is derived from unknown precursors. A dermoid cyst of the ovary, containing a large amount of material, was subjected to analysis. Squalene was found associated with cholesterol as a characteristic of the cyst lipids. Possibly cholesterol is derived from squalene or from fatty acids.

EFESKIRD, I.: *Liver changes in patients with gastrointestinal conditions.* (*Acta Chirurg. Scand.*, v. 93, p. 81, 1946).

Patients with nutritional disturbances associated with digestive tract disease, anemia, and hepatic or biliary duct disorders showed definite changes in liver histology. The changes were very much accentuated by subjecting the patient to surgery. The changes observed were those associated with either fat or glycogen deposition, those concerned with cell mitosis and configuration and those concerned with lymphatocytic infiltration processes and fibrosis.

ELIASHEVITCH, E. S.: *The hydrolytic and synthetic activities of liver lipase.* (*Biochem. J. Ukraine*, v. 17, p. 271, 1941).

The hydrolytic activity was expressed in terms of butyrase units while synthetic activity was determined as the amount of butyric acid transformed to higher lipids by a given amount of dry liver tissue. Synthetic activity in relation to lipolytic activity had a coefficient of 3.2 to 4.0 for adult rabbits and 3.5 to 5.0 for growing rabbits. The coefficient for rats was much higher, 10.2.

FENSTER, E.: *Hepatorenal syndrome in liver trauma.* (*Arch. klin. Chir.*, v. 205, p. 179, 1943).

Trauma of the liver may give rise to parenchymatous lesions of the kidney similar in character to those obtained by injecting either suspensions or autolysates of liver tissue. Presumably the injury to liver causes disintegration of tissue with the same result. Early diagnosis of kidney damage in cases of liver trauma is necessary so that insulin and glucose treatments and blood transfusions may be instituted. Four cases are reported.

GAVRILOV, R. F.: *Function of small intestine in excreting reducing substances.* (*Bull. Exper. Biol. Med. U. R. S. S.*, v. 19, p. 26, 1945).

Parenterally administered dextrose is excreted rapidly from iso-intestinal loops that have been denervated but not from non-denervated loops. Injection of sodium chloride, but not calcium chloride, resulted in an increased excretion of administered dextrose in the intestinal juice of normal dogs.

GUTMANN, R. A.: *Early diagnosis of gastric cancer.* (*Presse Med.*, v. 53, p. 150, 1945).

Early diagnosis was made in 18 cases of small gastric lesions and surgery was performed promptly. Only one of the operated cases died and showed metastatic extension to the liver.

HARTIALA, K. AND KÄRVOREN, M.: *Anoxia in relation to secretion of hydrochloric acid.* (*Acta Physiol. Scand.*, v. 11, p. 85, 1946).

With increase in altitude (and corresponding decrease in oxygen pressure) there was found in three human subjects a decrease in the secretion of hydrochloric acid. Administration of ammonium chloride the preceding day did not influence the secretion of acid. The reduction in acid secretion is probably due to the anoxia rather than the hyperventilation alkalosis.

KLEIN, E.: *Contact between colon and kidney: explanation of right-sided pyelitis.* (*Anat. Anz.*, v. 91, p. 225, 1941).

Measurement in 90 cadavers showed that the right kidney has about twice as much surface in contact with the colon as the left kidney. Pyelitis involving the right side is more common than pyelitis of the left side, perhaps because of the greater contact of the right kidney pelvis with the colon and direct transference of infection through the contact area.

KOSTER, K. H. AND TRALLE, D.: *Postoperative shock after gastrectomy.* (*Acta Chirurg. Scand.*, v. 93, p. 51, 1946).

Blood chemistry and hematologic conditions were studied in patients before and after subjection to gastric operations (26 for gastric ulcer, 37 for gastric cancer). Blood concentration was reduced in patients who survived the operation; this was a good prognostic sign. When the blood concentration was 25 per cent higher after operation the patient died (12 cases) even if hemoconcentration was later reduced to normal. Administration of fluids is necessary but cannot be undertaken on the basis of the plasma chloride concentration.

KRAVITZKAYA, P. S. AND LANDA, A. H.: *Fluoroscopy of the stomach in relation to age.* (*J. Pharmacol. Toxicol. U. R. S. S.*, v. 7, p. 27, 1944).

The preantral sphincter of the puppy is revealed fluoroscopically by barium sulfate contrast only after about the tenth day of life. Gastric emptying time is influenced by the age of the animal, being fastest in the younger puppy. The composition and consistency of the meal also influence gastric emptying time.

MALMEJAC, J. AND CHARDON, G.: *Effect of low atmospheric pressure on intestinal activity.* (*Bull. Soc. Biol., Paris*, p. 31, 1942).

Nembutalized dogs in a decompression chamber showed inhibition of intestinal motor activities when the pressure fell to the equivalent of 8000 to 9000 meters altitude. The inhibition is due to anoxia since depression of intestinal activity does not occur if the animal is allowed to breathe pure oxygen during the decompression.

ORLOVA, A. P.: *Effect of saliva on the digestive action of gastric juice.* (*J. Yanova-Lenina U., Kazan. U. R. S. S.*, v. 101, p. 54, 1941).

Foods were saturated with saliva and introduced directly into the stomach of the dog through a fistula. Starch-foods containing saliva had the most marked effect. The volume and acidity of the gastric juice were depressed by the presence of the saliva.

OURY, P. AND VERRET, A.: *Non-ulcerative duodenitis.* (*Arch. Malad. Appareil Digest.*, v. 34, p. 30, 1945).

Duodenitis is diagnosed with difficulty. Roentgenologic studies are helpful. A hazy bulbar contour may be indicative of duodenitis, especially if no niche is present. Surgical intervention is not favored. Treatment by bed rest, bland foods, bismuth subnitrate, tincture of belladonna and vitamins A and D are recommended.

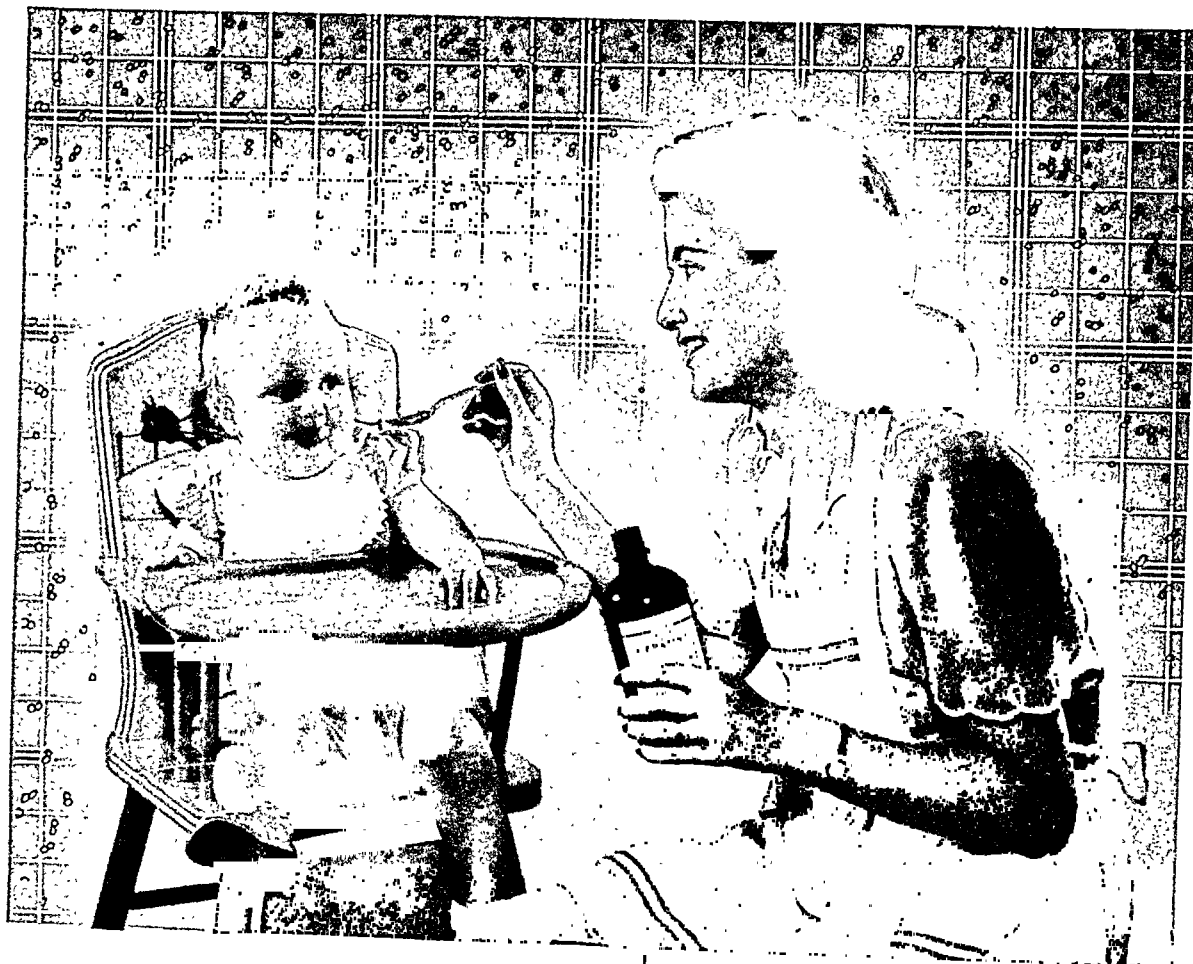
RASK-NIELSEN, R.: *The peptidase of the gland cells of the pylorus.* (*Comp. Rend. Trav. Lab. Carls.*, v. 25, p. 32, 1943).

Structural and chemical studies were made on alternate sections of pig's pyloric mucosa. The dipeptidase in the region of the surface and of the neck cells was constant and was found to be increased in the region of the chief cells. The tripeptidase increased from the surface epithelium towards the underlying muscularis mucosae.

RANDOIN, F.: *Polyncuritis produced by diets lacking trace elements (iron, manganese, iodine, aluminum).* (*Comp. rend. soc. biol.*, v. 138, p. 729, 1944).

Young rats were kept on synthetic diets containing all the known vitamin B fractions. The diet was adequate in all respects except that it lacked iron, manganese, iodine and aluminum. Although thiamine was present in abundance, the animals developed symptoms of thiamine deficiency. All four elements were necessary to prevent development of polynuritis: the absence of any one element was enough to bring about the polynuritis even though the other three elements were supplied.

Number 5 of a Series



ANEMIAS OF CHILDHOOD

Nutritional anemia
Idiopathic seborrhea
von Jaksch's syndrome

—the combination of ferrous iron, unfractionated liver and B vitamins effects a more powerful hemopoietic action than any form of iron alone—

HEPATINIC

—particularly suited for administration to children because of its pleasant flavor and easy administration—contains (per fluidounce): Ferrous sulfate 12 gr., Crude Liver Concentrate 60 gr., fortified to represent Thiamine Hydrochloride 2 mg., Riboflavin 4 mg., Niacinamide 20 mg., together with pyridoxine, pantothenic acid, choline, folic acid, vitamin B₁₀, vitamin B₁₁, biotin, inositol, para-aminobenzoic acid and other factors of the vitamin B complex as found in crude (unfractionated) liver concentrate.

The value of the crude (unfractionated) liver concentrate in Hepatinic is of the highest order, for all the erythropoietic principles are retained. In addition, this unique liver is subjected to a special enzymatic digestion process which converts it to a most readily assimilable form.

Tasting samples are available to all physicians upon request.

Elixir Hepatinic is supplied in bottles of one pint and one gallon

McNEIL

LABORATORIES, INC., PHILADELPHIA 32, PENNSYLVANIA

BEAUMONT S. CORNELL, *Editor*
Fort Wayne, Indiana

Editorial Office:
435 Lincoln Tower, Fort Wayne, Indiana

Editorial Council

CLINICAL MEDICINE—DISEASES OF DIGESTION

ALBERT FREDERICK RUGER ANDRESEN,
Brooklyn, N. Y.
J. ARNOLD BARGEN, Rochester, Minn.
ANTHONY BASSLER, New York, N. Y.
EDWARD B. BENEDICT, Boston, Mass.
JOHN MINOR BLACKFORD, Seattle, Wash.
LEON BLOCH, Chicago, Ill.
ARTHUR LEONARD BLOOMFIELD,
San Francisco, Calif.
RUSSELL S. BOLES, Philadelphia, Pa.
JOSEPH EDMOND DUBE, Montreal, Can.
EDWARD S. EMERY, JR., Boston, Mass.
GEORGE B. EUSTERMAN, Rochester,
Minn.
JULIUS FRIEDENWALD, Baltimore, Md.
HARRY GAUSS, Denver, Col.
FRANK D. GORHAM, St. Louis, Mo.
RUSSELL L. HADEN, Cleveland, O.
R. H. M. HARDISTY, Montreal, Can.

CHARLES LESTER HARTSOCK,
Cleveland, O.
BLAIR HOLCOMB, Portland, Ore.
HARRY G. JACOBI, New York, N. Y.
ALLEN A. JONES, Buffalo, N. Y.
CHESTER M. JONES, Boston, Mass.
CLEMENT RUSSELL JONES,
Pittsburgh, Pa.
NOBLE WILEY JONES, Portland, Ore.
JOSEPH WILLIAM LARIMORE,
St. Louis, Mo.
JEAN ROGER ARTHUR LeSAGE,
Montreal, Can.
B. B. VINCENT LYON, Philadelphia, Pa.
ERNEST PERRY McCULLAGH,
Cleveland, O.
CHARLES MARTIN, Montreal, Can.
LAY MARTIN, Baltimore, Md.

FRANCIS D. MURPHY, Milwaukee, Wis.
MOSES PAULSON, Baltimore, Md.
GEORGE M. PIERSON, Philadelphia, Pa.
MILTON M. PORTIS, Chicago, Ill.
MARTIN REHFUSS, Philadelphia, Pa.
VERNON C. ROWLAND, Cleveland, O.
ADOLPH SACHS, Omaha, Nebr.
LEON SCHIFF, Cincinnati, O.
HOWARD FRANCIS SHATTUCK,
New York, N. Y.
DANIEL N. SILVERMAN, New Orleans, La.
VIRGIL E. SIMPSON, Louisville, Ky.
ALBERT M. SNELL, Rochester, Minn.
HORACE W. SOPER, St. Louis, Mo.
CYRUS CRESSEY STURGIS,
Ann Arbor, Mich.
MARTIN G. VORHAUS, New York, N. Y.
FRANKLIN W. WHITE, Boston, Mass.
L. G. ZERFAS, Indianapolis, Ind.

NUTRITION

LLOYD ARNOLD, Chicago, Ill.
CLIFFORD JOSEPH BARBORKA,
Chicago, Ill.
REGINALD FITZ, Boston, Mass.
SEALE HARRIS, Birmingham, Ala.
HENRY L. JOHN, Cleveland, O.
HOWARD FRANK ROOT, Boston, Mass.
NINA SIMMONDS, San Francisco, Calif.
FREDERICK F. TISDALL,
Toronto, Ont., Can.

THERAPEUTICS

WALTER A. BASTEDO, New York, N. Y.

PARASITOLOGY

CHARLES F. CRAIG, New Orleans, La.
ROBERT HEGNER, Baltimore, Md.
KENNETH MERRILL LYNCH,
Charleston, S. C.
THOMAS BYRD MAGATH,
Rochester, Minn.
HENRY MELENEY, Nashville, Tenn.

ALLERGY

ALBERT H. ROWE, Oakland, Calif.
J. WARRICK THOMAS, Richmond, Va.

ROENTGENOLOGY

DAVID S. BEILIN, Chicago, Ill.
ARTHUR C. CHRISTIE, Washington, D. C.
E. N. COLLINS, Cleveland, O.
FREDERICK J. HODGES,
Ann Arbor, Mich.
FRANZ J. LUST, New York, N. Y.
WILLIAM H. STEWART, New York, N. Y.

GASTROSCOPY—ESOPHAGOSCOPY

JAMES L. BORLAND, Jacksonville, Fla.
E. B. FREEMAN, Baltimore, Md.
CHEVALIER JACKSON, Philadelphia, Pa.
RUDOLF SCHINDLER, Chicago, Ill.
PORTER PAISLEY VINSON,
Richmond, Va.

EXPERIMENTAL PHYSIOLOGY

BORIS P. BABKIN, Montreal, Can.
J. P. QUIGLEY, Memphis, Tenn.
A. J. CARLSON, Chicago, Ill.

IRA A. MANVILLE, Portland, Ore.
EDWARD J. VAN LIERE, Morgantown, W. Va.
M. H. F. FRIEDMAN, Philadelphia, Pa.

PSYCHIATRY AND NEUROLOGY

WILLIAM C. MENNINGER, Topeka, Kansas

ABDOMINAL SURGERY

ALBERT A. BERG, New York, N. Y.
HON. HERBERT ALEXANDER BRUCE,
Toronto, Ont., Can.
ROSCOE R. GRAHAM, Toronto, Can.

THOMAS M. JOYCE, Portland, Ore.
RUDOLPH MATAS, New Orleans, La.
EDWARD WILLIAM ALTON OCHSNER,
New Orleans, La.

NELSON M. PERCY, Chicago, Ill.
JAMES TAFT PILCHER, Brooklyn, N. Y.
CHARLES T. STURGEON,
Los Angeles, Calif.

SURGERY OF THE LOWER COLON AND RECTUM

LOUIS ARTHUR BUIE, Rochester, Minn.
JEROME MORLEY LYNCH,
New York, N. Y.

CLEMENT L. MARTIN, Chicago, Ill.
CURTICE ROSSER, Dallas, Texas

LOUIS J. HIRSCHMAN, Detroit, Mich.
FRANK C. YEOMANS, New York, N. Y.

ABSTRACTS OF CURRENT LITERATURE

M. H. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
*M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

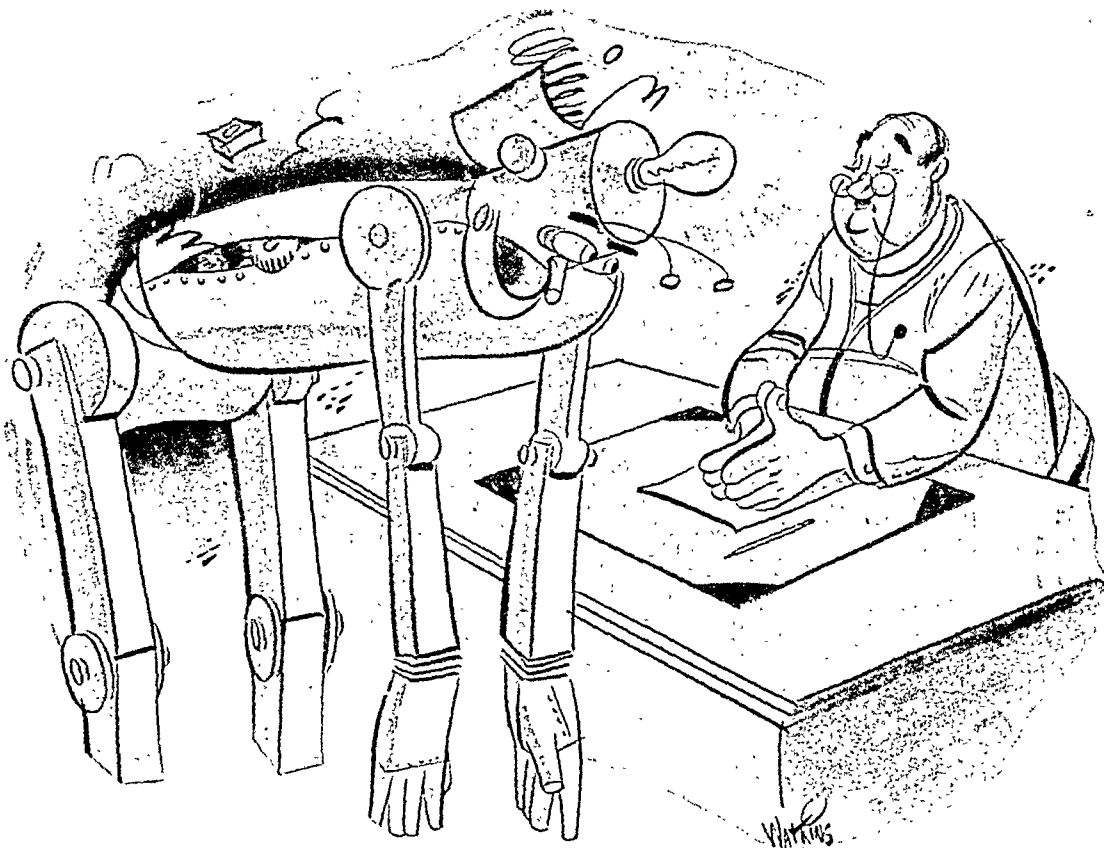
* With the Armed Forces.

FRANZ J. LUST, Regional Editor, 17 E. 89th St., New York City

Published Monthly at 114 E. Seymour St., Muncie, Indiana

Copyright, 1946, by the Sandfield Publishing Co., Editorial offices, 435-455 Lincoln Bank Tower, Fort Wayne, Indiana, in the United States. Volume 13, Number 10, October, 1946. Subscription price in U. S. A. and Canada, \$6.00 per year; Foreign, \$7.00 per year. Nothing that appears in the American Journal of Digestive Diseases may be reprinted either wholly or in part without permission, except for scientific reference purposes. Sandfield Publishing Co. assumes no responsibility for return of unsolicited manuscripts, and they will not be returned unless accompanied by stamped self-addressed envelope. Owners submitting unsolicited manuscripts assume all risk of their loss or damage. Until further notice, free medical journals will not be permitted to quote from this publication without approval of proof of copy. Entered as second-class matter at the post office at Muncie, Indiana, December 7, 1945, under the act of March 3, 1879.

Oh, Doctor!



"I DON'T KNOW WHAT TO DO, DOCTOR; I FEEL ALL RUN DOWN."

But seriously, Doctor . . . as you know, that "run down" feeling can be due to a lack of vitamin B₁ (thiamine)—the vitamin needed to convert carbohydrates into energy. In such cases, you may want to suggest that hot Ralston be included in the daily diet. Why? Because hot Ralston is 2½ times as rich as natural whole wheat in wheat germ—best cereal source of vitamin B₁.

TWO KINDS OF HOT RALSTON ➡

RALSTON PURINA COMPANY
Checkerboard Square, St. Louis 2, Mo.



The Oldest Periodical in Its Special Field on the Western Hemisphere

PUBLISHED MONTHLY AT
114 E. SEYMOUR ST.
MUNCIE, INDIANA

The American Journal of
DIGESTIVE DISEASES

Editorial Office:
SANDFIELD PUBLISHING CO.
435 LINCOLN BANK TOWER
FORT WAYNE, INDIANA

ANNUAL SUBSCRIPTION RATE \$6.00
SINGLE COPIES OF CURRENT ISSUE .80

General Office:
435-455 LINCOLN BANK TOWER
FORT WAYNE, INDIANA

THE AMERICAN JOURNAL OF DIGESTIVE DISEASES is published monthly. Its contents consist of original contributions — clinical and investigative — in the fields of digestive diseases, together with editorials, book-reviews, abstracts, monographs and proceedings of societies in these and allied subjects.

Subscription: This periodical is issued monthly, volumes beginning with the January 15th number each year. Subscription is by the year, but single copies of any current monthly issue are available. Subscription rates are, per annum, net prepaid \$6.00 (U.S.A. Funds) in United States and its possessions. The rate for foreign countries is \$7.00 (U.S.A. Funds) net prepaid. Prices of back volume or single back issues supplied upon application. Checks, drafts or money orders should be drawn to the order of the Sandfield Publishing Co. Unless subscribers definitely, in writing, request discontinuance after the expiration of an annual subscription, it is assumed that they still desire to receive the Journal and they will be billed for the succeeding volume.

Advertising: All plates and cuts for advertising insertions should be mailed to Publication Office, 114 E. Seymour St., Muncie, Ind.

Business Correspondence: All communications concerned with general business matters, changes of address, advertising, reprint, subscriptions, et cetera, are to be sent to the General Office, 116 E. Berry St., Fort Wayne, Ind.

Manuscripts: All correspondence relating to the submission, acceptance, rejection or the publication of manuscripts, as well as books and monographs for review, programs and reports of proceeding of society meetings and general communications must be addressed to Beaumont S. Cornell, M.D., 116 E. Berry St., Fort Wayne, Ind. Except where special arrangements are made, return, first-class postage must accompany manuscripts. Otherwise this office cannot be held responsible for the material sent.

All manuscripts must be typed, triple spaced, in black or blue ink and upon one side of standard manuscript sheets; the left margin should be 1½ inches in

Advertising Office:
360 N. MICHIGAN AVE.
CHICAGO
KNOEBBER & VINING
Advertising Representatives

width to insure proper editing. No manuscripts will be accepted for publication without consideration by the Supervising Editor and the majority approval of the particular group of the Editorial Council to which manuscripts will be submitted.

In manuscripts, bibliographic references should be according to the following arrangements:

1—Author's name, title of Reference, name of Journal containing reference, with volume, pages and year. References should be listed by number at the end of each article.

Six illustrations (or charts) are allowed per manuscript without cost. Illustrations in excess of six will be charged at cost to the author. All lettering should be distinctly printed and all charts and illustrations numbered, labeled with proper and easily understood descriptive notes. Each chart or illustration must bear the author's name, address and title of article of which it forms a part.

Reviews: The American Journal of Digestive Diseases will endeavor to feature reviews of books and monographs in its own and allied fields.

Authors and publishers desiring to submit material for review should forward it direct, fully prepared to the Editor at 116 E. Berry St., Fort Wayne, Ind.

Reviews will be wholly objective and unbiased since it is assumed by the Editor and the Editorial Council that the purpose of any review is to convey to readers the actual contents and value of the monograph or text-book under consideration. In this respect the Business Office and the Editorial Department of this Journal act wholly independently.

The American Journal of Digestive Diseases is interested in nutrition and the subjects of food, vitamins, minerals and hormonal metabolism. Authors are assured of as speedy publication of their submitted articles as possible, as no large backlog of MSS is ever kept on hand.

The contents of this Journal are fully copyrighted and material from it must not be used without the consent of the Editor. There is no objection to the use of quotations for scientific purposes, provided due acknowledgment is made, but the Publishers will not permit any quotations for commercial purposes.

Practical visualization of the normally functioning gallbladder is obtained simply and conveniently with PRIODAX.

PRIODAX

beta-(4-hydroxy-3,5-diiodophenyl)-alpha-phenyl-propionic acid

Containing 51.3 per cent iodine in firmly bound combination, PRIODAX "has no phenolphthalein radical in its composition and is totally unrelated to it."¹ Gastrointestinal by-effects—nausea, vomiting, diarrhea—are uncommon.

WITH ACCURACY

Single-dose cholecystography with PRIODAX, brand of iodoalphonic acid, permits objective evaluation of gallbladder function. Double doses or repeated doses are rarely required with this new and efficiently secreted contrast medium.

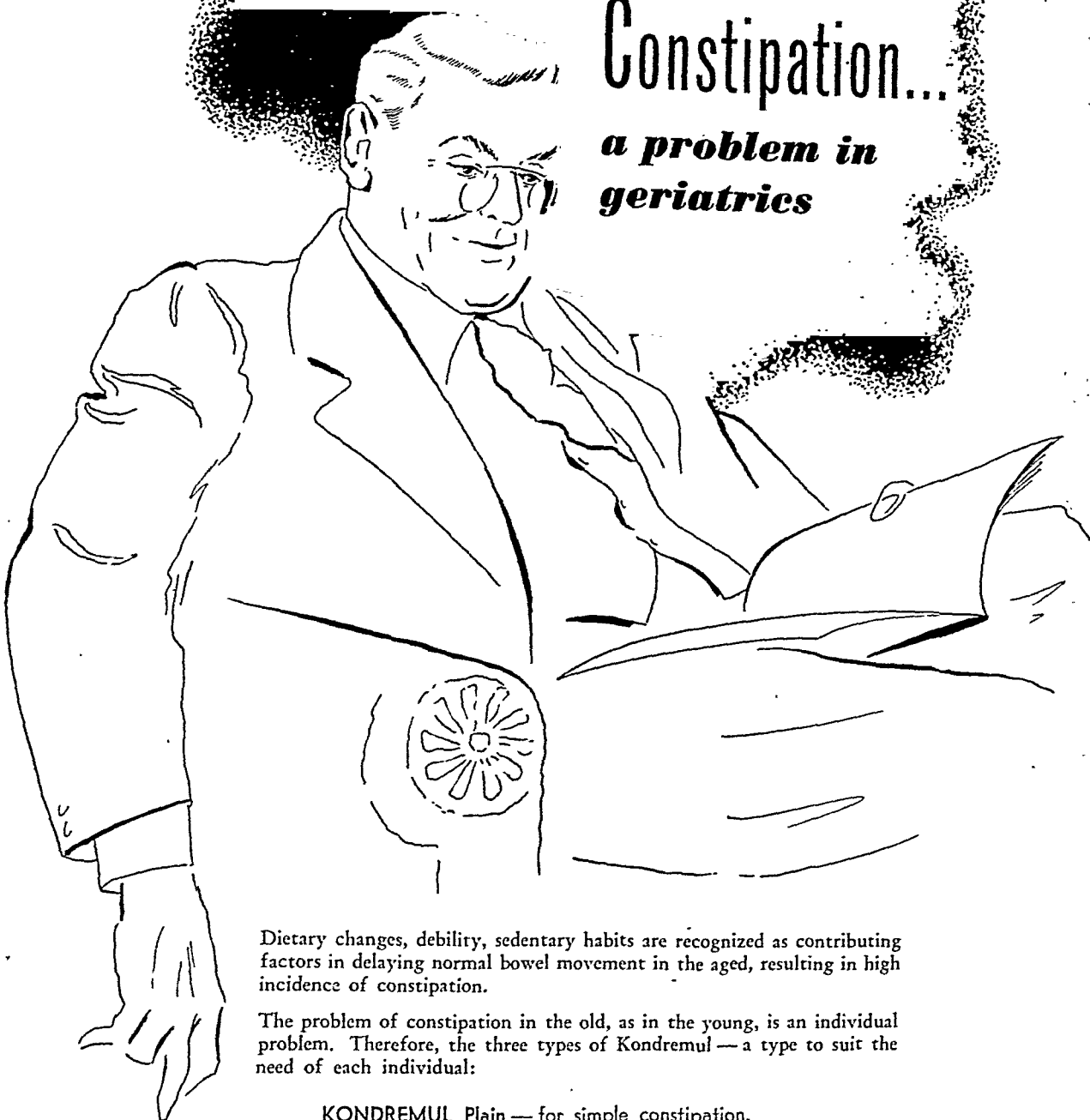
¹ J. Dannenberg, M.: Am. J. Roentgenol. 51:328, 1944.

Trade-Mark PRIODAX—Reg. U.S. Pat. Off.

CORPORATION • BLOOMFIELD, N. J.
IN CANADA, SCHERING CORPORATION LIMITED, MONTREAL

Constipation...

*a problem in
geriatrics*



Dietary changes, debility, sedentary habits are recognized as contributing factors in delaying normal bowel movement in the aged, resulting in high incidence of constipation.

The problem of constipation in the old, as in the young, is an individual problem. Therefore, the three types of Kondremul — a type to suit the need of each individual:

KONDREMUL Plain — for simple constipation.

KONDREMUL with non-bitter Extract of Cascara* —
for prolonged laxation.

KONDREMUL with Phenolphthalein* [2.2 grs. phenolph-
thalein per tablespoonful] — for the resistant case.

**Caution: Use only as directed.*

Canadian Producers: CHARLES E. FROSST & CO., Box 247, Montreal, Quebec.

THE E. L. PATCH COMPANY, BOSTON, MASS.

Special Diets

Needn't Be Dull!



**What a difference to the patient
when you vary the diet with Knox delicacies!**

THE psychological effect of tasty, appealing foods is generally recognized as an important consideration in planning diets for the sick.

With pure, unflavored Knox Gelatine, it's as easy for the family as it is for the experienced nurse to prepare a wide variety of interesting, attractive dishes that will appeal both to the patient's eye and palate...while obeying "doctor's orders"!

All-protein Knox is one of the

most versatile of foods for it can be combined with eggs, milk, fish or meat to make high protein dishes... or with fresh fruits and vegetables to make high-vitamin dishes. Special diets needn't be dull when they include delicious Knox delicacies!

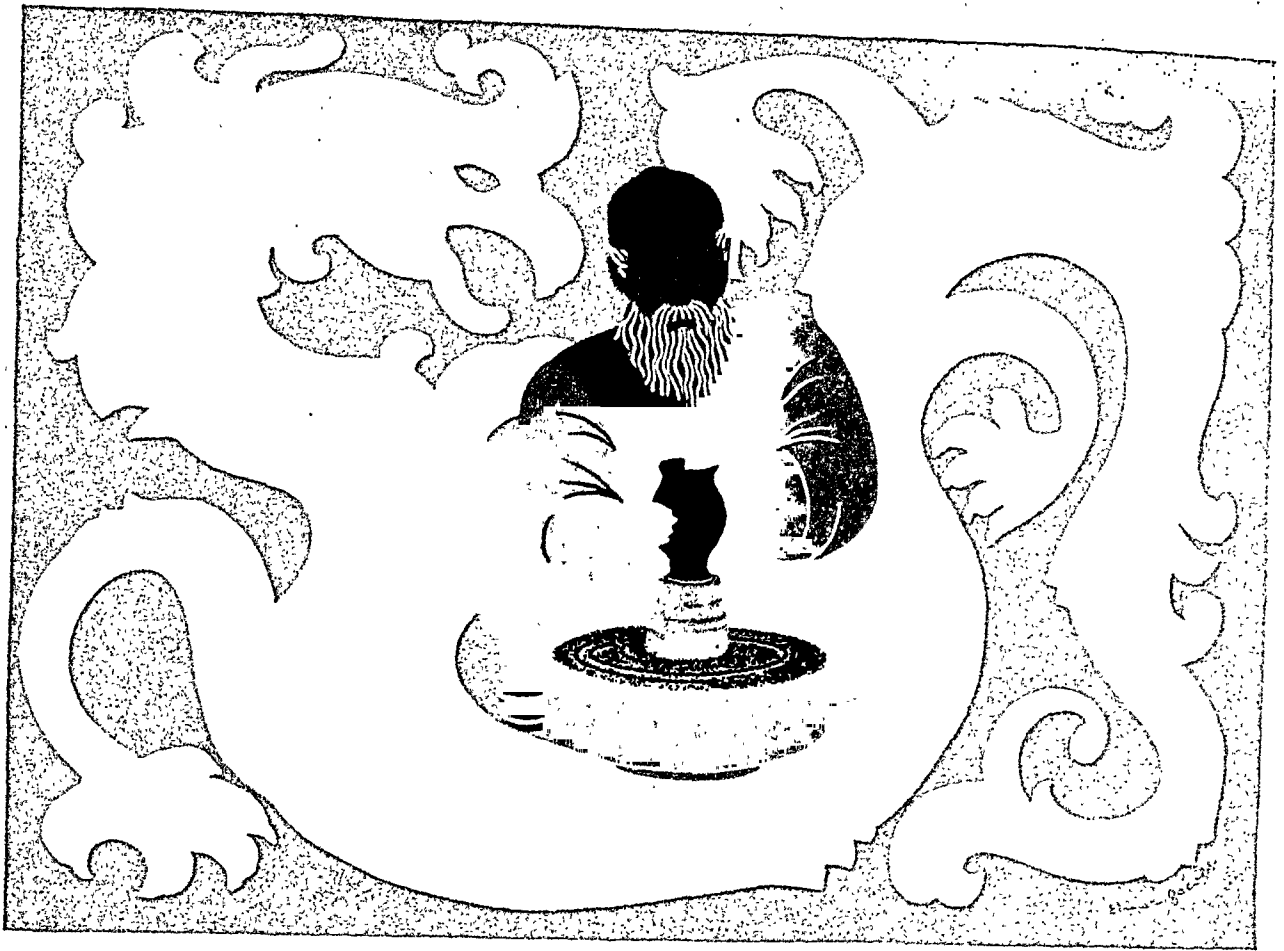
FREE Diets and Recipes

Specially prepared dietary booklets will be sent FREE upon request to Knox Gelatine, Dept. 475, Johnstown, N. Y.

KNOX GELATINE (U. S. P.)

PLAIN, UNFLAVORED GELATINE...ALL PROTEIN, NO SUGAR





White Magic

● Quality clays and skilled craftsmanship both have contributed to the creation of China's age-old record for fine porcelain and pottery. Since antiquity, the same kaolin used by the potter has been used by the Chinese for intestinal disorders. Magical powers were attributed to it for restoring normal bowel function. Scientific research has merely confirmed the efficacy of this prescription.

The excellent adsorptive properties of kaolin are combined with the astringent and antiseptic action of zinc phenolsulfonate in 'Pectocel' (Pectin and Kaolin Compound, Lilly). The pectin evenly suspends the colloidal kaolin, presenting it in its most active form. Pleasantly flavored to assure ready

acceptance by the patient, 'Pectocel' is an ideal combination for infectious and toxic diarrheas.

In nonspecific diarrheas, bacillary dysentery, or diarrhea caused by faulty diet or toxic irritants, the recommended dosage of 'Pectocel' is:

FOR ADULTS . . . Two or more tablespoonfuls, three or more times a day.

FOR CHILDREN . . . One or more teaspoonfuls, three or more times a day. The frequency of the dose may be increased if necessary.

Each fluid ounce of 'Pectocel' contains:

Pectin	4½ grs.
Kaolin90 grs.
Zinc Phenolsulfonate	1¼ grs.

In an aromatized aqueous suspension.

The Control of Muscle Spasm and Arthritic Pain Through Sympathetic Block at the Nasal Ganglion and the Use of the Adenylic Nucleotide

Contributions to the Physiology of Muscle Metabolism. Part II*

By
SIMON L. RUSKIN, M.D.

NEW YORK, N. Y.

THE STRIKING and dramatic relief of painful muscle spasm and arthritic pain through anaesthetization of the sphenopalatine ganglion by topical treatment presented a challenge for its interpretation. This was all the more pressing since behind the understanding of muscle spasm lay a series of clinical conditions so diverse as to appear on the surface completely unrelated. Thus the relief of sacro-iliac pain would hardly seem to be connected with a physiologic process such as essential hypertension and chronic osteoarthritis and acute arthritic pain. It was only through the recognition that muscle spasm affecting smooth muscle produces vascular disturbances quite as definitely as the cramp of striated skeletal muscle, that the relationship could be realized.

Instead of approaching the problem morphologically, by a study of the characteristics of histological differences under various chemical conditions, the problem was approached on the thesis that the underlying biochemistry of contractile elements which would characterize all muscle spasm would tend to be the same.

The functions of muscle activity were divided into three groups; one, reactions to reflex neurogenic impulses; two, autonomic neuro-effector systems; three, the chemistry of muscle contraction. Since this last phase underlies the basic physiology of nutrition the investigation developed some interesting new conceptions. These were described in my publication on "The Role of The Coenzymes of the B Complex and Amino Acids in Muscle Metabolism and Balanced Nutrition." I pointed out that the keystone of muscle metabolism was the adenylic nucleotide. It phosphorylates thiamin to cocarboxylase, thus making the biologically active coenzyme. Similarly, it phosphorylates riboflavin, and combined with niacinamide, it goes to form Coenzyme I and II. These are the factors that control cell respiration, for the coenzyme together with the amino acids of the protein portion form the respiratory enzymes. The term respiratory enzyme could be misleading since it is not a matter of lung respiration, but rather the enzymatic means whereby carbohydrate is gradually broken down by the stepwise removal of hydrogen and the liberation of energy. The oxygen is used through the adenylic nucleotide by the progressive build up of adenylic acid to adenosine triphosphoric acid and its graded break-down through adenosine diphosphoric to adenylic acid.

Were it not for these stepwise enzymatic processes utilizing oxygen and hydrogen gradually the energy of sugar ingested if suddenly released completely would be explosive in nature. This gradual chemical reaction constitutes "tissue respiration" and the "respiratory enzymes" conduct the orderly progress. It is the deficiencies of the elements of the respiratory enzymes that produce the classical pictures of vitamin deficiency. These respiratory enzyme deficiencies can occur from absence of any of the three portions of the respiratory enzymes; one, the vitamin segment such as thiamin, riboflavin, niacin; two, the coenzyme formed by the B Complex elements plus adenylic acid; three, the amino acids essential to make the specific protein of the respiratory enzyme. Only the combined presence of all elements gives a biologically active substance capable of conducting tissue metabolism.

Muscle metabolism requires, in addition to this energy releasing enzymatic setup, a substance that is uniquely capable of changing its molecular structure so as to alternately contract and return to its original form and utilizing for this purpose the energy released by tissue respiration. Such a substance is myosin, composed of a protein that is also bound to adenylic acid to form the enzyme adenosintriphosphatase. This appears to be the actual contractile element. In a previous paper quoted above, I described the electrical and physical factors involved in the transition from the contracted to the restored phase. The basic idea that develops from the chemical study of muscle contraction is the uniformity of the reaction for all types of muscle. The clinical implication of this conception is the intimate relationship between spasm of the large voluntary muscles of the arm, back and legs and those of the heart and blood vessels and the possible unity of the etiologic factor. It brings anginal spasm and hypertension into the same fold as lumbo sacral and shoulder spasm as well as arthritic pain. Practically, the therapeutic response appears to confirm this conception. Further confirmation lies in the success of the therapeutic use of the adenylic nucleotide as the iron salt (Ironyl). The increase in peripheral circulation and relief from fatigue following the intramuscular use of the iron adenylylate substantiates the role of the adenylic nucleotide in muscle metabolism. The factors that tend to throw the balance of the chemical reactions in muscle metabolism toward the maintenance of the contracted state with incomplete recovery are the keys to the therapy of muscle spasm.

*Part I appeared in the AMERICAN JOURNAL OF DIGESTIVE DISEASES, Vol. 13, No. 4, April, 1946.

Our next consideration is the reflex neurogenic factor in muscle spasm. In this field, the classical work of Crile introduced the conception of pathologic physiology. The idea of interrupting reflex autonomic factors by surgical attack on the adrenal sympathetic system dramatically demonstrated the ability to control muscular vaso-spasm in a lasting manner. Crile in a series of 386 operations, 234 being celiac ganglionectomies was able to show immediate readjustment of the blood pressure to normal or near normal levels. Smithwick has further demonstrated the same idea.

While these surgical procedures effectively interrupt this reflex neurogenic factor, I have found that similar results of a lasting nature may be obtained through blocking at the sympathetic sphenopalatine ganglion in the nose. In a previous publication on the "Neurologic Aspects of Nasal Sinus Infections," I pointed out the neurologic connections of the nasal ganglion. It remains to point out that the glosso-pharyngeal nerve which together with the middle and posterior palatine nerves supplies the tonsils, also carries fibres from the carotid sinus so that the extra-cranial control of cerebral circulation can be intimately tied up with nose and throat pathology and conversely we can influence not only the cerebral circulation in migraine but systemic circulation in essential hypertension. It is not a far cry from general vascular spasm to localized vascular spasm and arthritic pain. The relief of arthritic pain is so immediate and the resolution of joint swelling and improved motion in osteoarthritic joints following blocking of the sphenopalatine ganglion so rapid, that we must consider seriously the possibility that osteoarthritis is primarily a circulatory spastic phenomenon of the terminal circulation in the joint followed eventually by nutritional bone changes.

While Crile speaks of essential hypertension as a universal contraction of all the blood vessels of the whole arterial tree in the same sense that the arteries of the extremities become contracted in Raynaud's disease, he draws the analogy between a continuous sustained high blood pressure and a continuously cold extremity with gangrene in Raynaud's disease. He describes it as a non-adaptive excessive activity of an organ which is functioning normally and cannot stop to readjust itself. It is as if one set his automobile accelerator at high and could not bring it back to normal rate. While this theory is interesting, still it must rest on balance between the chemical neuro-effectors such as acetylcholine and sympathin and adrenine, and the chemical factors such as the choline esterase, gonadal hormones and vitamin coenzymes which influence them. The role of neostigmine in the inhibition of choline esterase has recently received renewed attention.

While all these considerations have possibly thrown some light on muscle contraction, we still have to consider what constitutes muscle spasm. Most important in this connection is the observation made by Ramsey and Street that a muscle fibre stretched beyond its nor-

mal relaxation does not return to its initial length. Experimentally, they found that if a fibre is allowed to shorten below 60-70% of the resting length, a striking change in its properties may be observed, and for convenience, they have characterized this change of properties as a change of state and labeled it the "delta" state. In particular, if a fibre is shortened until it is only one-fifth or one-third as long as its resting length and is then re-extended, a new length tension diagram is obtained which at its maximum develops about one-half the tension it could before the shortening took place. The excitability mechanism is unaffected, and the responses are propagated responses and not local responses.

The most striking change in the properties of fibres in the delta state is concerned with relaxation. If a normal fibre is allowed to shorten, it will actively return to resting length of its own accord after cessation of the stimulus provided it is not allowed to shorten more than one-third of its resting length. No weight is required to stretch it back to resting length. There is in fact some active process of relaxation. If a fibre is converted to the delta state, the active process of relaxation is abolished and the fibre remains shortened at whatever length it was allowed to shorten to.

Whether the initial outpouring of sympathin that followed in the wake of a sudden excitement, in the pull on a muscle in an attempt to lift a heavy weight, or a sudden turn, is the cause of the undue extension of the muscle fibre, the end result seems to be a pathologic physiology that is difficult to restore spontaneously. No answer has as yet been found to the correction of the delta state of myofibril contraction. Its elucidation will bring with it a new era in physiology, and a most gratifying contribution to therapy. Sympathetic block seems to provide one of the first steps in this direction, and the relaxation of lumbo sacral and neck and shoulder spasm is truly dramatic. Sympathetic block at the nasal ganglion appears to permit normal acetylcholine action. The restoration of muscle tone appears to be further heightened by parenteral use of the adenylic nucleotide as the iron salt. This would tend to indicate that adenylic acid is related to active relaxation as well as to active contraction.

Experimental records were made of a muscle fibre brought into the delta state by two summated twitches only in this case the fibre was so short (resting length 2-3 mm.) and therefore relatively stiff so that it could maintain itself horizontally when held at one end. The record clearly showed that there is an active process of relaxation occurring in the normal fibre which is abolished in the fibre in the delta state.

There are many other characteristics of this delta state which are of interest, thus there is a morphological as well as a physiological basis for these changes in properties. Briefly, if a delta state fibre is examined microscopically at lengths less than resting length, the striations are not all equidistant, but are made up of bands of close striations alternating with bands of stri-

ations a normal distance apart. Upon stretch of the fibre, the bands of close striations pull out until at resting length the striations are all equidistant and normally arranged. During stimulation of such fibres, there is a continual interchange of the bands of close and normally distant striations and the whole picture looks much like the contracture bands reported in the literature of muscle. A possible explanation appears in my earlier paper on the "Role of The Coenzymes in Muscle Metabolism."

It is only in the light of this experimental work that we can begin to understand not only persisting muscle spasm such as sacro-iliac, stiff neck and shoulder, but also arthritic contractures and poliomyelitis contractures and spasm. When translated to smooth muscle, we can understand vasoconstriction of the vascular tree with resultant essential hypertension.

Fenn points out that even at rest, the muscle fibre possesses some outstanding peculiarities. Unlike other cells, the muscle cell can be stimulated to contraction, thereby bringing about an almost instantaneous transformation of its shape and cytology, its mechanical and electrical state, its temperature, chemical composition and rate of respiration.

At the desire of the investigator, a series of new chemical reactions can be thrown into activity in an orderly and reproducible manner. This sudden transformation so produced may properly be called a controlled explosion. The muscle is a self-cocking explosive machine with a convenient trigger. The explosion turns chemical potential energy into mechanical energy that can lift weights or do the most delicate movements. The forces developed in a muscle "explosion" are of amazing magnitude. Some of the muscle tendons transmit forces of the order of half a ton. Single fibres of the muscle can also be isolated in Ringer solution, and the resulting threads of muscle contract vigorously for days and exert relatively large forces.

Along with the development of mechanical energy there is a development of electrical energy. In the muscle as in the nerve this provides a mechanism for conduction of a contraction wave from one end of the muscle to the other. We are just beginning to appreciate that this electrical change can be resolved into various parts comparable to the spike and the after potentials of nerve and to learn what other processes are associated with these potentials. Of particular significance are the newly discovered potentials associated with activities of the myoneural junctions.

It is by way of the sympathetic that we must search for the influence on the electrical potentials of muscle induced by anesthetics, particularly the local anesthetics. This is especially evident in shock. The application of a local anesthetic such as cocaine, nupercaine or even novocaine can create a sudden change of muscle tone ranging from relaxation to complete flaccidity so that even the ability to move can be abolished. This has proven to be particularly important in treatment since

the dosage may determine the point of relaxation sufficient to relieve the patient of his arthritic or sacro-iliac pain or easily be pushed further to the stage of flaccidity which may be alarming to doctor and patient. Since the dosage varies with the severity of the individual attack, experience is the best guide and under dosage the better judgment for the beginner. The total dosage is less than for the usual eye treatment.

The problem of muscle tension is intimately bound up with muscle mechanics and represents a new chapter in physiology, largely the result of the work of A. V. Hill. He showed that the faster the muscle shortens, the greater the drain upon its energy supply for purposes of shortening and the less the energy available for maintaining tension. Thus sudden straining at heavy weight or a misstep can result in tension imbalance.

Our third division of the investigation into muscle physiology, the neuro effector system, brings with it also a therapeutic answer. I have already described the chemical factors which play a role at the myoneural junction such as acetylcholine and sympathin and adrenaline. The detailed study of these factors is the subject of another paper on "Vascular Dynamics." We saw that the adenylic nucleotide played the basic role in muscle dynamics and thermo dynamics. Now we find that therapeutically the anesthetization with cocaine, novocaine or nupercaine of a sympathetic nerve center, the spheno-palatine (nasal) ganglion is followed by immediate generalized relaxation of muscle spasm not only of smooth muscle such as the arterial tree but of striated skeletal and syncytial cardiac muscle. This effect is not obtained by systemic administration of the anesthetic solution in the dosages used, but is profound when applied directly to the sympathetic nerve center. The degree of this effect can readily be compared with surgical intervention on the adrenal medullar sympathetic system.

Cannon and Rosenblueth point out that cocaine and pre-ganglionic denervation enhance the mechanical while depressing the electrical responses of muscle. This is precisely what is needed in muscle spasm, and if we consider the proof of the pudding to be in the eating, we have it in the therapeutic success. Similarly the injection of the iron salt of the adenylic nucleotide, ferrous adenyate increases the mechanical response of the muscle fibre through making available immediately the energy rich phosphate and enhances the capacity of the muscle to overcome the spasm, possibly by active relaxation.

Between the onset of these studies in 1924 and the present day, a continuous investigation of these phenomena has been made and the number of cases can easily be numbered in the thousands. I have selected for this report only the last fifty cases to avoid undue repetition. Broadly, the indications for this type of therapy may be listed as:

1. Painful muscle spasm of the sacro-iliac, lumbago, torticollis type.

2. Acute arthritic and chronic osteoarthritic pains.
3. Hypertension and peripheral vascular spasm.
4. Coronary spasm.
5. Migraine and hemicrania.
6. Herpetic pain.
7. Spasmodic hiccup or sneezing.
8. Menstrual pain.
9. Ureteral colic.
10. Intercostal neuralgia.
11. During the period of muscle spasm in poliomyelitis this treatment offers a most fruitful field for careful application.

Many of these have been described in my earlier case reports.

In many of these cases the adenylic nucleotide was used as the Ferrous adenylate (Ironyl) 30 mg. This was administered intra-muscularly deep in the gluteal

muscle. Care was taken to avoid being in a vein since the vascular dilatation that follows can be sufficiently sudden on intravenous injection to cause syncope. In all cases calcium ascorbate injections were also given. Without the spheno-palatine ganglion block neither the adenylate nor the calcium ascorbate relieved the spastic state.

SUMMARY

1. Muscle spasm and arthritic pain can be controlled directly through influencing the sympathetic at the spheno-palatine ganglion.

2. Increasing the supply of the energy rich phosphate bond in the form of the Ferrous adenylate (Ironyl) is an aid in the correction of the delta state of the myofibril.

3. The dramatic nature of the results is its greatest handicap.

Name Age Sex			Diagnosis	History	Treatment and Results
J.A.	41	M	Lumbo-sacral spasm (sacro-iliac)	Sacro-iliac for last two years. At present having severe pain; more intense on bending. No headache, sore throat or post-nasal drip. Unable to work.	After 1st ganglion treatment patient able to move and bend with ease. Given 1 ganglion treatment the following day. No return of pain. Patient returned in 2 weeks for check-up. No return of pain; able to continue with his work as window cleaner.
O.B.	44	F	Chronic Arthritis with deformity	Arthritis in both hands and wrists, and stiffness of neck and shoulders. Had rheumatism in childhood. Tonsillectomy in 1918 with some improvement. Both hands and wrists show marked deformity. Severe pain in arms, also in back of neck. Has had to discontinue her work as seamstress because of inability to hold needle or sew. Unable to raise arms to horizontal level.	Given 1 ganglion treatment e. o. d. for 5 days. At that time patient states there is improvement of sleep; formerly dreamed a lot and is a very restless sleeper. Swelling of joints diminished; pain in neck gone; marked increase in motion of both hands, joints and arms. Given 1 ganglion treatment every other week for 5 weeks. During this period, patient returned to work. At present she is able to sew and use her hands without pain or any recurrence of pain. Swelling and deformity of wrists and knuckles almost gone.
L.H.	55	F	Cervical and lumbo-sacral spasm, spheno-palatine ganglion neuralgia	Pains in neck, head and shoulder. Left arm has been broken at elbow and feels cold. Pain in back reaching to sacro-iliac region. Sleeping poorly. Headaches worse when lying down. B. P. 128/82. Headaches over left eye, back of ears and back of head.	Received 1 ganglion treatment every day for 4 days. After this period patient states definite improvement in headaches. Pain in back and sacro-iliac region entirely relieved. Then 1 treatment every 3 days for 4 treatments. After this period, patient reported entire relief of pain and all previous complaints.
R.Z.	26	F	Rheumatic Arthritis with deformity	Rheumatic arthritis since 1940 with swelling and deformity in ankles, knees and elbows. Extreme difficulty in walking. X-ray of ankles negative. Running low grade temperature in evening accompanied with occasional chills. Continuous muscle pains in arms and legs. Has had series of gold injections with reaction of itching and rash. Had no improvement in arthritis.	After 1st ganglion treatment slight improvement in walking. Given 1 ganglion treatment e. o. d. for 10 treatments. After this period of treatment, pain in knees and ankles greatly diminished. Walking with less difficulty and without the shuffling gait she has acquired; since, given 1 ganglion treatment twice a week with loss of swelling on each return visit. Ankles appear to be gradually returning to normal size. Patient was practically bedridden at time of onset of treatment. Now is able to travel in subway and able to practice dancing. Each treatment supplemented by Ironyl and calcium ascorbate.
H. VanW		F	Chronic Arthritis with muscle spasm	In 1909 had severe pain like cramp in right side of hip. Hospitalized for 6 weeks. At that time leg contracted and shortened. At present suffering a great deal of pain in right hip with extreme limitation of motion of right leg. Present condition for 4 years. Difficulty in climbing steps.	Immediate results with 1st ganglion treatment. Walking with less difficulty. Given 1 ganglion treatment e. o. d. for 6 treatments. Walking greatly improved and going up steps much easier. Given 1 ganglion treatment each week for 6 weeks. At end of last treatment, patient appeared to be walking with greater ease. Able to raise leg to 90° while lying down. Able to move hip with less pain. Patient unable to raise leg more than 2 inches horizontally before treatment. Received Ironyl and Calcorbate with each treatment.
I.G.	61	M	Myocarditis; Angina Pectoris	Pain in chest with coronary condition for 1 year; intermittent, chiefly at night. Relieved by taking nitroglycerine. Also has pains in shoulder and left arm. Had manipulation of arm under general anesthesia which was followed by coronary pain. Occasional headaches. History of asthma for many years.	Ganglion treatment given with relief of coronary pain. Returned in 3 days stating that during that time pain did not return. Six days after initial treatment, patient was relieved of precordial attacks. No return of pain in 10 days' time. Received Ironyl and Calcorbate injections. Had return of precordial distress after cessation of treatments.

Name	Age	Sex	Diagnosis	History	Treatment and Results
M.H.	45	F	Renal colic	Severe pain in back, painful and frequent micturition. Diagnosed as renal colic by family physician.	1 ganglion treatment given with immediate relief of pain. Admitted to hospital. Given 1 ganglion treatment at hospital with relief of pain. Six hours after treatment patient expelled urethral stone spontaneously.
S.K.	61	M	Lumbo-sacral spasm	About 12-15 years ago, he lifted something heavy and had severe pain in back. Has had pain in both legs and small joints of hands and shoulders since. Wearing steel brace at present, prescribed by orthopedist.	Immediate relief with 1st ganglion treatment. Discarded brace. Given ganglion treatment each day for 3 consecutive days. No return of pain in back. Complete relief of pain in legs and small joints. Brace discarded entirely. Each ganglion treatment supplemented by Ironyl and Calcium Ascorbate injections.
S.M.	48	M	Torticollis	About 10 months ago he developed stiff neck, diagnosed as "wry neck." Received diathermy with some relief. Nine months ago had attack of spasm of left leg. Was relieved by injection into nerve of leg. Still has severe pains in neck and back. Occasional frontal headache.	After 1st ganglion treatment felt immediate relief of pain. Given treatment on 2 consecutive days. Greatly relieved after each treatment. No return of pain. Return visit to office 1 week after last treatment, patient reported no return of pain in back or neck. Able to touch toes with no disturbance to back. Discharged, completely relieved.
Sgt. D.S. (marine)	34	M	Lumbo-sacral spasm (sacro-iliac)	Was overthrown from jeep on Saipan, landed weight on left foot, twisting body. Three days later muscle in left lower back and left gluteal region "tied up" in spasm. Left hip restricted. Patient hospitalized in Honolulu. Given novocaine injection in back and gluteal muscle, also diathermy, rest and x-ray. Diagnosed as "possible ruptured disc." Returned to U. S. and hospitalized. At that time patient was walking bent over from waist, legs shook, slightest cough or sneeze brought on great pain. Muscles in back, hip, buttock and leg still in spasm and restricted in movement. Could not bend forward. Going down stairs legs could hardly hold body weight and shook. "Nerves in left leg jumping" continuously. Deep seated pain in hip. Bone fusion operation had been suggested. Belt and brace worn without help. Took some treatments from chiropractor with some relief but still has weakness, discomfort on standing, stiffness in getting up quickly, pain in left hip and gluteal muscle. Coughing and sneezing causing distress in hip and lumbar region.	Given 1 ganglion treatment with immediate relief. Able to bend without pain. Belt and brace discarded. 1 ganglion treatment given e. o. d. for 6 treatments with more relief. Able to walk and bend with no pain. Pain in back, hip and muscles completely relieved. Patient discharged in 2 weeks as cured. 1 month later patient wrote stating that he has had no return of attacks and has completely recovered. Now back on active Army duty with Marines.
Dr.D.R.	32	M	Chronic Arthritis	Onset in January 1942 with pain in hip extending up spine. Was diagnosed in Army as Marie-Strumpell Disease. Last August developed diarrhea followed by stiff neck and swelling of knees and ankles with elevation of temperature. This spread to chronic rheumatoid involvement of small joints. Has had some improvement on high vitamin therapy. Right ankle and left knee are swollen. Some pain in neck. E. K. G. normal. No bowel studies recently. X-ray negative. Tried prostigmin for neck spasm without relief. Walking with difficulty.	Immediate relief with 1st ganglion treatment. Walking easier. Given 1 ganglion treatment each day for 3 consecutive days with immediate relief after each treatment. Given 1 ganglion treatment e. o. d. for 4 treatments. Swelling of knees subsiding. Able to stand longer, walking without pain. 1 ganglion treatment each week. Swelling of knees lessening at each visit. Patient in better physical and mental condition. Gaining weight. Sleeping well. Each treatment supplemented by Ironyl and Calcium Ascorbate injections intramuscularly. Patient has returned to medical practice.
H.V.B.	59	F	Lumbo-sacral spasm (sacro-iliac)	5 months ago patient fell down 1 flight of stairs. Sustained no fracture, got up and walked. For last 2 weeks unable to walk. Walking with extreme pain and difficulty and in bent over position. Has been to osteopaths and chiropractors, without relief. Has had heat and baking treatment without relief. At times pain so unbearable that to get relief she has to bend entirely over. After pain subsides she is able to straighten up. Has high blood pressure.	After 1 ganglion treatment patient able to walk with very little difficulty. Given 1 treatment every day for 6 consecutive days. Pains return and has some difficulty in walking each a. m. After treatment the following day and each a. m. thereafter pain seemed less than previously. Then given 1 treatment e. o. d. for 8 treatments and 1 every week for 2 weeks. Pain gradually became less after each treatment. After last treatment, patient states she has no pain nor has she had any return of pain from 1 week's treatment to the next. Sleeping better. Patient has had no recurrence in 1 year.
K.W.	25	F	Chronic Arthritis	Has had generalized arthritis for last 4 years. Has pain in arms and legs. Several months ago pain so severe she had to be carried. Walking with great difficulty. Joints of fingers and toes swollen. Unable to open or close hands. Unable to grasp anything. Has had series of gold injections. Was treated for 2 years at Medical Center.	Given 1 ganglion treatment with immediate relief. After 2nd ganglion treatment following day, she was able to bathe her baby for first time in 3 years. Received daily treatment for 2 weeks. Then once weekly for 2 months. Is able to drive car, dance, and has knitted two handbags for my nurses.

Name	Age	Sex	Diagnosis	History	Treatment and Results
F.E.	49	M	Arthritis Deformans (Marie-Strumpell Disease)	For last 8 years has had severe arthritis. For last 5 years has been bent over so that his head is at a 70° angle to body. Formerly had terrific pains in back, now only in neck. Sleeps on side. Onset in small of back. Diagnosed as stomach ulcers. Then pain spread to back. Started stiffness of body 5 years ago. Can bring arms only to horizontal position. Unable to turn head. Only able to see a person's feet. Has to be led to his destination.	With 1st ganglion treatment patient able to turn head some. Able to see window of room, first time in 5 years. Given 1 ganglion treatment each day for 2 weeks. At end of this period, patient able to shave himself, which he was unable to do previously. Able to go anywhere without depending on anyone to lead him. Patient returned in 2 months and continued same treatment for 2 weeks, then returned in 2 months for 2 more weeks of treatment. At present, patient able to turn head with very little difficulty. Also able to see people while speaking to them. Previously unable to do this. Body now at a 35° angle.
F.T.	39	F	Chronic Arthritis	Arthritic pains in hands and feet. Swelling of hands and feet. Difficulty in walking, swelling of joints of fingers; 7 years ago was "crippled up" and bed-ridden. Had tonsils and several teeth extracted with some relief.	With 1 ganglion treatment, patient able to walk without pain; given 6 ganglion treatments for 6 consecutive days. After each treatment pain became less and was able to move more easily during day. Sleeping better than previously. Unable to sleep before because of pain. Then given 1 treatment e. o. d. for 3 treatments, then 1 treatment each week for 3 weeks. At time of discharge swelling entirely gone from joints of fingers. Sleeping well. No return of pain.
G.R.	39	F	Lumbo-sacral spasm (sacro-iliac)	Backache in lower part of back for about 6 weeks extending into right leg. Has been in bed for 2 weeks. Was relieved while in bed but still has pain when standing. Right hip appears to be much lower than left, throws right hip out when walking. Walking painful.	After 1 ganglion treatment, able to walk without pain. Ganglion treatment given following 2 days. Pain in leg lessened after each treatment. Then treatment e. o. d. for 2 treatments, then 1 treatment each week for 3 weeks. At end of 3rd treatment, patient appears to be walking much better and hip appears to be straightening. At time of discharge hips straight, body erect. No pain while walking. No return of backache.
C.S.	33	F	Lumbo-sacral spasm (sacro-iliac)	Severe pain in back for last 3 days. This is 3rd attack, each usually lasting several months. Pain some times radiating to thighs. During attacks, hip is usually thrown out of position to left, disfiguring patient. Onset with cold, 3 days ago.	With one ganglion treatment pain relieved in back; able to walk with less difficulty. Given 1 treatment daily for 5 days. Pain gradually diminishing. At end of 2 weeks pain entirely gone with no return. Walking with ease.
Dr.M.M.	46	M	Intervertebral disc injury	Slipped on deck of boat 4 years ago followed by sacro-iliac pain for about 2 years. Since last year has had increasing lumbo-sacral pain.	Spheno-palatine ganglion treatment afforded only very transient relief. After 3 treatments there was no improvement. Patient went to Mayo Clinic where intervertebral disc operation was performed with excellent results.
L.B.	54	F	Cervical and Shoulder spasm	Stiffness of neck and shoulder muscles, on and off for 4 years.	Given ganglion treatment with immediate results. Able to move neck and shoulder without pain or discomfort. No return treatment needed. No return of pain in 3 months.
C.A.	50	M	Cervical and Shoulder spasm	Stiffness of neck muscles and arm. Had similar attack 2 years ago. All teeth extracted with no relief of pain. Seen by MD. who recommended cast to neck and shoulder. Given treatment by osteopath. Sleeps poorly.	Ganglion treatment given with relief. Able to move arms with very little pain. Returned next day with little pain in arm. Ganglion treatment given with immediate relief. After 5 ganglion treatments over 5 consecutive days, pain entirely relieved from neck and shoulders. No return of pain.
Lt.H.A.	28	M	Lumbo-sacral spasm	Pain in back on and off for 3 months. Has had stiff shoulder for 8 years.	Given 1 ganglion treatment with immediate results. Returned following day with some pain. Ganglion treatment relieved pain entirely. No return. Discharged. Shoulder stiffness completely gone.
M.A.	51	F	Lumbo-sacral spasm (sacro-iliac)	Pain in sacro-iliac region for 6 weeks. Has had pain off and on for several years. Radiates to right leg, but is now confined to sacro-iliac region. No headache or sore throat.	Relieved immediately after 1 ganglion treatment. Returned following day with some pain when bending. Ganglion treatment given every 2nd day for 5 treatments. Each return visit, reported little recurrent pain. On fifth visit, no pain at all. Discharged.
G.Dec.	35	F	Shoulder muscle spasm	Tooth extracted 1 week ago, developed severe pain in right antrum. 3 days later developed pain in left arm. Unable to move it out or back. Able to raise arm with great pain. Carrying arm in sling for relief.	After 1 ganglion treatment, patient able to move arm but with pain. Following day after treatment, able to raise arm with less discomfort. Returning following day with very little pain. Able to move arm with ease.
P.DeR.	40	M	Cervical and Shoulder muscle spasm	Onset, stiff neck 3 weeks ago. Became acute 10 days ago, radiating to left arm. Formerly had pain at base of neck. Unable to move left arm. In continuous pain on motion.	Ganglion treatment with results. Able to move arm and neck. Given treatment every day for 5 consecutive days. Greatly relieved, able to move arm with no discomfort. No return of pain.

Name	Age	Sex	Diagnosis	History	Treatment and Results
S.B.	42	M	Lumbo-sacral spasm (sacro-iliac)	Has had severe lumbago for last 3 days. Unable to walk or bend. Had similar attacks few years ago. Had to be supported to get into office.	Ganglion treatment with immediate relief. Able to walk without support. Returned the following day with slight pain in back but able to bend with little pain. Given ganglion treatment with immediate relief. Returned following day with no pain. No return of pain in 1 week.
Dr.L.A.	60	M	Lumbo-sacral spasm (sacro-iliac)	Severe sacro-iliac sprain, duration 2 weeks. Unable to walk or bend. Pain at all times regardless of position.	Given 1 ganglion treatment with immediate relief. Able to move and bend without pain. Given ganglion treatment following day with same results. No return of pain.
S.C.	48	M	Shoulder muscle spasm	Pain in left arm extending to forearm for last 9 months. Pain chiefly at night, not a sharp pain, but drawing and heaviness. Pain on stretching arm back. No headache.	Given 1 ganglion treatment with immediate relief. Given ganglion treatment for following 2 days. Entirely free from all pain, able to move arm. Sleeping well.
L.C.	32	F	Cervical and Shoulder muscle spasm	Stiffness of neck, left shoulder, arm and left side of body last 10 months. Pain when walking.	After 1 ganglion treatment, patient able to move neck and shoulder with ease. Less pain when walking. Given 1 treatment each day for 3 consecutive days. Able to move neck and walk without difficulty. No return of pain or stiffness. Local tonsillectomy later.
J.C.	21	F	Dysmenorrhea	Acute menstrual pain.	Given 1 ganglion treatment while having pain. Pain entirely relieved. Patient able to go to rehearsal. Dancing 1 hour after treatment. This treatment was given each month for 6 months.
R.C.	34	F	Traumatic Sprain of Ankle	Sprained right ankle, swollen, pain when walking. Unable to put weight on foot.	Given 1 ganglion treatment, pain relieved. Patient able to walk and work for remainder of day. Given 1 treatment in evening of same day. Ice applied at night to relieve swelling. 1 treatment next day with very little return of pain.
M.C.	63	F	Lumbo-sacral spasm (sacro-iliac)	Pain in back for years. Pain when walking and climbing stairs. Wearing heavy corset for support.	Given 1 ganglion treatment with immediate relief. Able to climb steps with no discomfort. 1 treatment given on following day. Pain entirely gone. No return of pain after 1 month.
S.E.	47	F	Cervical and Shoulder muscle spasm (bursitis)	Stiff shoulder for 15 years, getting worse. 3 years ago had bursa of shoulder tapped with some relief. No pain has returned, associated with pain in back and radiating down leg. Has stiff neck often. No headaches.	After ganglion treatment, patient able to move neck and shoulder. Pain in back and leg lessened. Given 3 ganglion treatments over period of 1 week. Greatly relieved. No recurrence of pain in back, legs, neck or shoulder.
M.H.	50	F	Lumbo-sacral spasm (sacro-iliac) sciatica	Hospitalized. Unable to walk because of severe pain in lumbo-sacral region and right leg.	Given 1 treatment at hospital. Patient able to get out of bed and walk without pain immediately. Came to office next day and was given treatment for 2 consecutive days with almost complete relief. Able to get around and attend to her affairs.
W.J.	48	M	Lumbo-sacral spasm (sacro-iliac)	Acute pain in back. Very painful when moving and walking. Adhesive strapping. Has been taking baking treatment without relief.	Given 1 treatment with immediate relief. No return of pain. Strapping removed.
A.I.	47	M	Cervical and Shoulder muscle spasms (bursitis)	Pain in shoulder and right arm. Painful to close hand. Has had pain on and off for about 3 months.	After 1 treatment, patient able to close hand and move arm without discomfort. Given 1 treatment each day for 4 days. Pain entirely relieved.
F.H.	50	F	Chronic Arthritis	Stiffness of back of neck since last summer. X-rays show some arthritic changes. No headache.	Given 1 ganglion treatment with fairly good results. Thereafter 1 treatment each day for 5 days. Improvement but some stiffness of neck still persisting, although patient reports she is able to sleep much better than before.
E.P.	47	F	Chronic Arthritis	Pain in left hand for last month with some swelling, radiating to left arm and shoulder.	After 1 ganglion treatment, patient able to close hand without difficulty. After 3 treatments patient able to move arm and shoulder without pain. Swelling also subsiding. Given 6 treatments in all with no return of pain or swelling.
Dr.H.P.	55	M	Lumbo-sacral spasm (sacro-iliac)	Severe pain in back, more acute when moving or walking. Unable to bend, unable to operate. Pain radiating to shoulder when moving arms.	Given 1 ganglion treatment with immediate relief. Able to move without difficulty. Able to operate same day. No return of pain or any discomfort.
G.P.	55	M	Lumbo-sacral spasm (sacro-iliac) sciatica	Pain in back last 5 weeks. Difficulty in getting up. Pain radiating down right leg. Had backache, similar attack 3 years ago. Sudden onset.	Given 1 ganglion treatment. Patient was able to bend and touch floor. Given 1 treatment every day for 5 days. Backache entirely relieved. No return of pain.
W.D.	49	M	Lumbo-sacral spasm (sacro-iliac)	Pain in sacro-iliac region. Pain when bending and climbing steps. Unable to walk more than a city block. Suffering sacro-iliac pain for 2 years.	Patient given ganglion treatment with immediate relief. Able to bend and move without pain. No return treatment necessary. Was able to march in church parade following day after 1st treatment.

Name	Age	Sex	Diagnosis	History	Treatment and Results
H.H.	36	M	Lumbo-sacral spasm (sacro-iliac)	Pain in back 2-3 weeks. Onset while in bath tub, became worse after coughing spell. Pain worse while sitting. Top of thigh painful. Pain in region of lateral cutaneous nerve of thigh. Wearing belt for support. Was hospitalized for 2 weeks.	Given 1 ganglion treatment with immediate relief. No return of pain. Received 3 daily treatments then once weekly for 2 weeks.
M.H.	51	F	Chronic Arthritis	10 years ago had pain in arms and unable to move them. Relieved by sulphur baths. Lately, joints of big toes very sore and tender. For last week has had pain in left shoulder and left sterno-clavicular joint. Has feeling of coldness and numbness in legs.	Given 1 ganglion treatment with relief. Able to move arm and shoulder without pain. Given 1 treatment each day for 1 week. Greatly improved. Feeling normal circulation returning to legs. Able to move shoulder without discomfort.
E.H.	50	F	Cervical and Shoulder spasm (bursitis)	Stiff right shoulder for last week. Pain starts in shoulder and radiates to forearm and fingers, had similar attack 2 years ago, diagnosed as bursitis. No headache.	After 1 ganglion treatment, patient able to move neck and shoulder. Given 1 treatment each day for 3 days, then 1 treatment every 2nd day for 1 week, then 1 each week for 2 weeks. At end of treatments, patient able to move neck and shoulder without discomfort. No return of pain.
H.H.	58	M	Cervical and Shoulder spasm (bursitis)	Has had pain in left arm for last 3-4 months. Had diathermy without relief. Had general anesthesia to move arm, but no results.	After 1 ganglion treatment, patient able to move arm with some pain. Given 1 treatment each day for 3 days. After 3rd. treatment, patient able to move arm without difficulty. No recurrence after 1 month check-up.
Dr.C.R.	48	M	Lumbo-sacral spasm (sacro-iliac)	Pain in back. Pain more acute when moving. Unable to stand to operate. Painful when moving arms.	After 1 ganglion treatment, immediate relief. Able to bend without pain. Able to operate same day with no recurrent pain.
H.K.	45	F	Lumbo-sacral spasm (sacro-iliac)	Last week moved from chair and felt sudden pain in sacro-iliac region. Now unable to move. Has some one to dress her. Pain when standing and sitting. Wearing belt and adhesive strapping.	Immediate relief with 1 ganglion treatment. Strapping and belt removed. Given 1 treatment the following day. No return of pain. Discharged.
B.S.	54	M	Lumbo-sacral spasm (sacro-iliac)	Pain in right sacro-iliac region for last three weeks, radiating down right leg. Today unable to get out of bed. Walking with cane. X-rays show no bone disturbance. Taking baking treatments. Back strapped.	Complete relief with 1 ganglion treatment. Slight return of pain during night, but able to get out of bed. Adhesive strapping removed. Given 1 treatment each day for 4 days with entire relief of pain.
J.B.	45	M	Neck and shoulder spasm (bursitis)	Pain in left arm last few days. No previous attacks. Unable to raise left arm. Pain is constant.	Given 1 ganglion treatment with immediate relief. Able to raise arm without difficulty. Pain relieved. No return of pain following day.
A.O.	45	M	Lumbo-sacral spasm (sacro-iliac)	Pain in sacro-iliac region with pain when bending and stooping. Uncomfortable when sitting or standing. Wearing belt for support.	After 1 ganglion treatment, patient completely relieved of pain. Able to move with ease. No return of pain or discomfort.
G.P.	31	M	Lumbo-sacral spasm (sacro-iliac)	Since March 1942 had back pains in lumbar region, radiating into buttocks and thigh. Has slept on board since August 1942. Wearing brace for support.	After 1 treatment, patient discarded brace. Given 1 treatment each day for 5 days. Entirely relieved. Able to sleep through night. Board removed from bed. No return of pain.
P.O.	45	F	Lumbo-sacral spasm (sacro-iliac)	Sacro-iliac pain, intermittently for 5-6 years. Today had severe attack.	Given 1 ganglion treatment with immediate relief. Able to move without pain. Given 1 treatment each day for 4 consecutive days. Complete relief of pain.
J.L.	39	M	Lumbo-sacral spasm (sacro-iliac)	Pain in back. Onset 1937 and intermittent since. Pain comes on with motion, bending, stooping. No neck or shoulder pains. Unable to play golf.	After 1 ganglion treatment, patient was able to move, bend and stoop with ease. Given 1 ganglion treatment every day for 3 days. Complete relief of pain. Check-up 3 months later. No return of pain. Playing golf again.
L.L.	38	M	Lumbo-sacral spasm (sacro-iliac)	About 4 years ago patient received an injury to his back. Since, has had severe sacro-iliac attacks. Yesterday had severe onset of pain in back, unable to move. He gets no relief from any position. Sleeps on board with no benefit.	1 ganglion treatment with relief. Able to touch floor with finger tips. No pain involved. Slight return of pain during night, but not as severe, and able to sleep. Returned for treatment for 3 consecutive days with no return of pain after each treatment. Returned for check-up in 6 weeks. No return of pain. Able to move with ease.
S.A.	48	M	Cervical and lumbo-sacral spasm	Pain in back and arms. Has had repeated attacks for 2 years almost continuously.	Given 1 ganglion treatment with immediate relief. Pain completely gone. No return of pain.
A.C.	32	F	Intercostal Neuralgia (intercostal spasm)	"Pleurisy pain" in back, numbness in hands and thighs. No headache.	After 1 ganglion treatment, patient states numbness in hands greatly relieved. Able to move hand, pain in back gone. 2 days later returned for treatment with entire relief from pain.
B.C.	37	F	Lumbo-sacral spasm (sacro-iliac)	Severe pain in back. Unable to bend. Pain when walking. Sacro-iliac region strapped with adhesive.	1 ganglion treatment. Patient able to move, bend and walk with comfort. No follow up treatment necessary.

Name	Age	Sex	Diagnosis	History	Treatment and Results
F.C.	36	M	Lumbo-sacral spasm (sacro-iliac)	Severe pain in back. Unable to bend or move. Patient wearing belt for support. Hospitalized for a time. Was scheduled for spinal fusion operation, suggested for relief.	Patient given 1 ganglion treatment with immediate relief. Given ganglion treatment for following 2 days with definite improvement each day. Then given 1 treatment each week for 3 weeks. Has not worn support since first treatment. Patient now playing tennis and is swimming with no ill effects. No return of pain.
H.C.	32	M	Lumbo-sacral spasm (sacro-iliac)	Intermittent backaches for the last 2 years. Severe for last 2 weeks. Pain worse when sitting. No headache. Patient wearing belt for support.	After 1st ganglion treatment, patient able to move freely without discomfort. Given treatment following day with very good results. Returned 1 week later. Reported no return of pain. Is not wearing support at present.
Pfc. J.R.B., son of a middle west Surgeon	20	M	Muscle tonus disturbance	Was wounded in neck by shell which entered the larynx on right side passing through neck on the left. When seen in consultation at the request of the Surgeon General at Halloran Hospital, patient had been unable to elevate his left arm and suffered continuous pain in left hand, arm and shoulder. A partial cervical sympathectomy had been performed on left side with slight transient improvement. He had also suffered a gun shot wound of right hand with loss of 2 fingers. Patient thus had tube in his trachea, right hand in splint, and unable to use left arm for either cleaning tube or feeding himself.	Treatment was carried out at the Halloran Hospital through the courtesy of the Surgeon General. Anesthetization of spheno-palatine ganglion was followed by immediate relief of muscle spasm and pain. Patient was able to lift food to his mouth. After 2nd treatment, patient was able to feed himself and had definite relief of pain. He received subsequent treatment of spheno-palatine ganglion as demonstrated to the Colonel in charge and was in condition to be sent home after two weeks. Within 1 month he was able to drive a car. The spheno-palatine ganglion treatment was done under the supervision of Dr. Ruskin.
L.L.	46	M	Hamstring spasm (sciatica)	Had right sciatica in 1934, recurring 6 weeks ago. Still having pain. Pain on walking, bending. Sleeping disturbed. Unable to get out of bed for 3 weeks with ease. Unable to sit down without pain. coughing brings on pain in right leg and left arm.	Immediate relief after 1st ganglion treatment. Slight return of pain next day, but walking with less discomfort. Given ganglion treatment every day for 6 consecutive days. Slight return of pain, but gradually becoming less, then complete relief of pain. Able to move, walk, bend without pain. Sleeping improved. No return of pain. Each treatment supplemented by Ironyl and Calcium Ascorbate injections intramuscularly.
T.T.	50	M	Lumbo-sacral spasm (sacro-iliac)	Severe pain in sacro-iliac region. Unable to bend. Severe pain when walking. Back strapped with adhesive.	After 1 ganglion treatment, patient able to bend and touch floor with finger tips. Pain entirely relieved. Patient given treatment 2 days later. No return of pain.
S.O.	47	F	Osteo Arthritis Hypertrophic	Numbness in right hand. Stiffness in both shoulders and cramp in both thighs. No headache. Pains in shoulders worse last few days. Severe cramps in legs. No nasal discharge. Hands show swelling of knuckles and wrists.	After 1st ganglion treatment, numbness in hand, pain in shoulders relieved. Given ganglion treatment every 3rd day for two weeks. After series of treatment, patient showed definite improvement in hands, arms, legs and back. Continued treatment once each week for 4 weeks. No return of pain in that length of time. Marked increase in mobility of hands and arms with regression of swelling.
C.W. Ref. by Lib. Mut. Ins. Co.	56	M	Muscle tonus disturbance	4 months ago fell from a ceiling, a height of 16 feet, landing on cement floor. Was unconscious and taken to hospital. Had laceration of right forehead which was sutured. He also had abrasions of right temple and upper part of lobe of right ear. Does not know of any bleeding from ears, nose or throat. X-rays were taken while hospitalized. Now complains of stiffness of neck. Cannot turn head to right or left. Neck aches constantly. Unable to raise arm to horizontal level. Occasional headaches and dizziness.	After 1st ganglion treatment, had immediate relief. Able to move neck and raise arm easily. Given 3 ganglion treatments for 3 consecutive days with relief. Then given 1 ganglion treatment every 2nd day for 3 treatments. Definite improvement after each treatment. No return of pain. Able to move neck and raise arm after 1st treatment. Discharged after 8 ganglion treatments. Although patient had been listed as completely disabled by Compensation Commission before treatment, he returned to work and waived total disability.
H.G.	36	M	Lumbo-sacral spasm (sacro-iliac)	10 days ago, after lifting heavy carton, felt sharp pain in sacro-iliac region, which left after about half hour. 3 days later pain recurred and is becoming worse. Unable to walk, sit or lie in bed in comfort.	Given 1 ganglion treatment with immediate relief. Able to move about without pain. Given 1 treatment daily for two days. No return of pain. Complete relief.
M.G.	44	M	Lumbo-sacral spasm (sacro-iliac)	About 1 week ago, while working, suddenly felt severe pain in sacro-iliac region. Was unable to move. On bending head, felt severe pain in sacro-iliac region. Unable to walk without pain.	After 1 ganglion treatment, patient able to move and bend with ease. Given ganglion treatment on 3rd day following initial treatment. No return of pain following treatment.
J.F.	40	M	Lumbo-sacral and Hamstring spasms (sacro-iliac) (sciatica)	Pain in back and right leg for 1 month. Unable to walk, becoming more severe.	1 ganglion treatment with immediate relief. Able to stand erect and walk without pain. Given 1 treatment each day for 6 consecutive days. Slight return of pain each day but gradually lessening. After 10 treatments, no return of pain.

Name	Age	Sex	Diagnosis	History	Treatment and Results
A.F.	65	M	Lumbo-sacral and Hamstring spasms (sacro-iliac) (sciatica)	Onset: cold 5 days ago followed by severe pain in back radiating down left leg. Walking with difficulty. Using cane.	Immediate relief after first ganglion treatment. Walking without use of cane. Given treatment for 3 consecutive days. Walking improved but still has slight pain. Given treatment in 10 days following. Greatly relieved.
H.S.M.	44	M	Lumbo-sacral spasm (sacro-iliac)	Pain in back, sacro-iliac region. Has had osteopath treatment. Has repeated recurrence, usually following colds. Has dry throat, repeated colds.	Given 3 ganglion treatments for 3 consecutive days. Immediate relief after 1st treatment. Pain in back relieved immediately following initial treatment. After 1 week, return visit, reported no recurrence of back pain. Each treatment supplemented by intramuscular injections of Ironyl and Calcium Ascorbate.

The entire series of cases received injections of Ferrous adenylate (Ironyl) and Calcium ascorbate (Cal-scorbate) after each speno-palatine ganglion treatment.

The injections were given intramuscularly in the gluteus, the calcium on one side and the Ironyl on the other.

REFERENCES

1. Blair, H. A.: Muscle Excitability. Biol. Symposia, Vol. III.
2. Block, R. J. and Bolling, D.: Nutritional Opportunities with Amino Acids. J. Am. Dietetic Assn., Vol. 20, Sept. 1943.
3. Bozler, E.: Action Potentials and Conduction of Excitation in Muscle. Biol. Symposia, Vol. III.
4. Cannon, W. B. and Rosenbluth: Autonomic Neuro-Effector Systems. The Macmillan Company, 1937.
5. Eccles et al: Electric Potential Changes Accompanying Neuro-Muscular Transmission. Biol. Symposia, Vol. III.
6. Fenn, W. O.: Muscle. Biol. Symposia, Vol. III.
7. Gordon and Sevringhaus: Vitamin Therapy in General Practice. The Year Book Publishers, 1942.
8. Hober, R.: Physical Chemistry of Cells and Tissues. Blakeson Co., 1945.
9. Meyerhoff, Otto: Significance of Oxidation for Muscular Contraction. Biol. Symposia, Vol. III.
10. Porter, V. R.: The Role of Vitamins in Energy Transformations. J. Am. Dietetic Assn., Vol. 19, No. 7, July 1943.
11. Rosenbluth, A.: Conduction in Smooth Muscle. Biol. Symposia, Vol. III.
12. Ruskin, S. L.: I. Studies on Parallel Action of Vitamin C and Calcium. Am. J. Dig. Dis., 5:408, 1938;
II. Studies in Calcium Metabolism: Further Contribution to Comparative Studies of Physico-Chemical Properties of Gluconate and Citratate of Calcium and of Vitamin C. Ibid., 5:676, 1938;
III. Mechanisms of Nephrosis in Sinusitis in Children. Acta Paediatrica 16, 249, 274, 33;
IV. Nucleic Acid and Nucleotide Therapy in Nasal Diseases; Contributions to Study of Chemical Aspects of Nasal Diseases. Arch. Otol., 22:172, Aug. '35.
V. Influence of Vitamin C on the Antihistamine Action of Various Drugs. Arch. Otol., 36:853-873, Dec. 1942.
VI. Adenylic Acid in The Treatment of Agranulocytosis and Mucous Membrane Lesions. Am. J. Dig. Dis.
VII. The Therapeutic Use of The Amino Acid. Histidine in Allergy and Shock. "Histidine as a Factor in Histamine Epinephrine Balance;" Am. J. Dig. Dis., Vol. II No. 7, July 1943.
VIII. High Dosage Vitamin C in Allergy. Am. J. Dig. Dis., Vol. 12, No. 9, Sept. 1945.
IX. The Role of the Coenzymes of the B Complex Vitamins and Amino Acids in Muscle Metabolism and Balanced Nutrition. Am. J. Dig. Dis., April, 1946.
13. Ruskin, S. L. and Jonnard, R.: Etudes Physico-Chimiques. Compare due Gluconate, due Sel de Calcium et de La Vitamine C. Compt. Rend de Biol., 28:266-268, 1938.
14. Ruskin, S. L. and Katz, E.: Therapeutic Action of Nucleotides; Treatment of Whole Blood Picture with Ferrous Adenylate. Ann. Int. Med., 9, 11, 36, 1549, 1560, May '36.
15. Wright, Samson: Applied Physiology. Oxford Univ. Press, 1941.

Physiological Derangements in Organic Disease of the Intestinal Tract

By

SAMUEL STANDARD, M.D.*†

NEW YORK, N. Y.

THE FUNCTION of the gastro-intestinal tract is primarily the storage, conversion and absorption of food to meet the nutritional requirements of the animal organism. The immediate importance of organic disease of the tract may be measured by the extent and severity of interference with the maintenance of these nutritional requirements. In obstructive lesions the interference with transportation of its contents explains the clinical picture. In inflammatory lesions without obstruction it often becomes difficult to account for the symptomatology purely on the basis of the organic lesion itself. The morbidity and often the critical fac-

tor in death may be, and often is, widely removed from the organic source, and can be accounted for only on a functional basis. The patient may die in uremia with normal kidneys, in convulsion with no cerebral damage, or may show a diffuse endocrinological breakdown with a normal set of endocrine glands. It becomes increasingly necessary to understand what the disease does as well as what the disease is.

Neurologically the gastro-intestinal tract is an interdependent unit stimulated by the cranio-sacral and inhibited by the thoraco-lumbar autonomic fibers. In the normal the peristalsis setup in the colon immediately following a meal is responsible for the habit of defecation. The reflex vomiting seen in inflammatory intestinal lesions is an example in reverse of the same integration of function. One would expect to find functional involvement mediated through the autonomic

*Presented before the New York Surgical Society, New York Academy of Medicine.

†From the Departments of Surgery and Physiology, New York University College of Medicine and the General Surgical Service, Montefiore Hospital.

Submitted March 30, 1946.

system in segments of the intestinal tract anatomically remote from the organic lesion.

Such a set of circumstances had been well established as operating in vascular organic lesions which, too, are autonomically innervated. Thrombophlebitis of the femoral vein induces edema, pain and ischaemia of the leg. It was thought that all of these could be explained on the basis of the blocked vein and adjacent lymphatics until Oschner and DeBakey (1) showed that by a para-vertebral block in the lumbar area all of these signs may disappear in twenty-four hours without in any way relieving the organic block that exists. It was then postulated that the signs were the result of a reflex vaso-spasm of the peripheral arterioles mediated through the thoracolumbar autonomic chain. The organic lesion constituted the receptor organ for the reflex, the sympathetic fibers and chain, the afferent and efferent arcs, and the arteriolar musculature, the effector organ. Since then it has been shown that the ischaemia of an arterial thrombosis is only partly due to the organic block and in great part produced by the reflex vaso-spasm induced. Here, too, sympathetic block increases the blood supply to the limb without altering the organic thrombus in the main artery. The most dramatic example of this, published by Volpito (3), is the restoration of function in a hemiplegic extremity by stellate ganglion block on the side of a cerebral thrombosis or embolus proving that the cerebral ischaemia can be relieved by breaking the reflex arteriolar vaso spasm induced by the organic lesion.

The same principle is involved in the improvement seen following autonomic cardiac denervation by alcohol or by surgical resection. Here too, the peripheral arteriolar spasm in the myocardium induced by the organic coronary thrombosis may be sufficiently relieved to increase the blood supply to the tissues not in the field of the actual infarct. Such autonomic denervation not only relieves pain but may actually increase myocardial vascularity.

Many clinicians have been struck by the weight loss, anemia, hypoproteinemia and vitamin deficiencies of relatively mild intestinal lesions. An excellent example of this is the gastro-jejuno-colic fistula. It was once thought that the profound cachexia that often accompanies this lesion could be explained on the basis of food being transferred from the stomach, a non-absorbing organ, to the colon, another non-absorbing organ (except for water); the entire small intestine being side-tracked the patient absorbed nothing from the ingested food. Since then it has been established that the fistula is usually a small one, that little if any food finds its way into the colon directly from the stomach, that most of it does traverse the entire length of small intestine, and yet weight loss is profound. *The inflammatory lesion at the fistula sets up an irritable focus which reflexly induces a hyperperistalsis in the small intestine of sufficient intensity to carry food through it with such speed as to allow practically no time for absorption.* A preliminary proximal colostomy side-tracks the infectious colonic contents away from

stomach and jejunum at the fistula. The acute inflammatory process subsides and though the fistula still exists, as proven later at operation, the reflex hyperperistalsis of small gut slows down sufficiently to allow adequate absorption. The improvement shown by these patients is often so marked that some refuse definitive surgery when it is later offered to them.

Ulcerative colitis is known to be a most debilitating disease yet here too a lesion involving rectum and sigmoid with relative freedom of the remainder of the colon from organic disease will induce profound systemic effects. These can be attributed to the reflex effects upon the small intestine. Gastro-intestinal series demonstrate the speed with which the small intestine transports its contents from stomach to colon. Early in the disease the barium may be in the cecum in thirty minutes.

True it is that water and minerals and proteins and blood are lost from the colonic mucosa. Yet with an intact small intestine one begins to wonder why replacement becomes impossible and one begins to understand why ileostomy fails to control the debility induced by the disease so long as the organic lesion continues to constitute the irritable focus for a hyperperistalsis which prevents adequate absorption.

The same principle may be applied to the relatively small lesions seen in regional ileitis. The diversity of surgical opinion on whether to resect or side-track the lesion rests on the differing responses of the organic lesion when it is defunctionalized. If the lesion heals by the side-tracking procedure no more surgery will be required. If it fails to heal, its reflex effects will continue to be a source of morbidity although it is anatomically no longer a factor.

Tuberculous ileitis induces somewhat the same picture and needs to be dealt with in the same way.

It is rare that a nutritional deficiency can be attributed to a single factor. Mackie (4, 5) has shown that usually the deficiencies are multiple. Once established the function of the small intestine may be variously disturbed. This part of the tract is emphasized because upon it, almost alone, falls the responsibility for adequate absorption and the maintenance of nutritional requirements. Early in nutritional deficiencies functional absorption is interfered with by hyperperistalsis; later actual organic pathology of the mucosa and myenteric plexuses have been demonstrated by Gordon. When this has occurred nutrition cannot be maintained even with slowing of propulsion of its contents. Thus a vicious cycle is set up. The functional derangement limits absorption which in turn induces a nutritional deficiency which further aggravates the already existing interference with proper absorption.

Many disturbances related to chronic intestinal disease states have been emphasized in the recent literature. They include hypoproteinemia and vitamin deficiencies. To these completely reported by Golden and by Mackie may be added the rarer and more generalized manifestations such as hormonal deficiencies and resultant in-

fantalism in the young, alterations in mineral metabolism particularly calcium loss and calculus formation, and production and maintenance of anemic states.

The great importance of the maintenance of a constant and adequate protein content has been emphasized in both the medical and surgical clinical literature as well as in the preclinical fields of physiology and biochemistry. A survey of the biological defects that appear when the body is deprived of its most important building materials, either because of inadequate intake or excessive loss reveals a wide distribution of signs and symptoms. That these signs may be attributed solely to the hypoproteinemia is questionable. Many of the intestinal changes have been reproduced in animals by simple plasmaphoresis, in the nephroses as demonstrated by Prendergrass (7) and with disorders of the liver; all three being associated with hypoproteinemia.

The list of manifestations induced by hypoproteinemia is an impressive one, it includes water retention, calcium mobilization and depletion, alterations in liver function, in wound healing, in intestinal motility, in the production of anemia, and in multiple vitamin and hormonal deficiencies.

The most important role of the plasma proteins is the maintenance of the constancy of the physical state of the plasma. In their absence or diminution the fluid balance between the blood and the intercellular tissue spaces and serous cavities is disturbed. Water retention in hypoproteinemic states has long been recognized. The combined oncotic pressure of the 7 grams of protein per 100 cc. of blood is 30 mm. Hg. It is this force which keeps fluid within the vascular bed against the hydrostatic pressure tending to push it out. Elman (8) suggests that in speaking of protein deficiency it would more nearly present the chemical pattern to define it as "hypoalbumenia" rather than hypoproteinemia. The albumin molecule is about $\frac{1}{4}$ the size of the globulin molecule and is the first to be lost and in most instances the only plasma protein lost. Note that in Case 1 the plasma protein fell from the normal (7 Gms. % with an A-G ratio of 4.5-2.5) to a total of 3.7 Gms. %. The inverted A-G ratio is due almost entirely to albumin loss with globulin practically unchanged. Each gram of albumin per 100 cc. of plasma exerts an oncotic pressure of 5.5 mm. Hg. each gram of globulin per 100 cc., a pressure 1.4 mm. Hg. From this it becomes plain that the albumin fraction is responsible for 85% of the total osmotic tension of the plasma proteins. With this in mind edema levels are reached because of an albuminemia in every instance. The loss of all the globulin from normal plasma would induce a fall in osmotic tension of lesser magnitude than the loss of one gram of albumin. This point deserves emphasis since albumin solutions are now available for parenteral use.

A negative nitrogen balance is the rule in chronic ulcerative colitis with progressive breakdown of body protein. Unlike fat and carbohydrate there are no available stores or reservoirs of protein in the body. There are at least three causes for protein reduction in

ulcerative colitis. First, there is the direct loss from the ulcerated areas. Secondly there is the decreased absorption in the small intestine due, in the early stages, to hyperperistalsis with its speedy transit and evacuation of unassimilated contents. Later there is faulty absorption due to organic diseases of the mucosa. Thirdly there is the increased caloric need due to hyperpyrexia and increased metabolic rate associated with anorexia which limits the actual intake. This combination of forces often reduces proteins to critical levels.

Another effect of hypoproteinemia which is often considered an isolated occurrence, is calcium depletion. There are three chemical factors that determine calcium solubility in serum. 1. A portion (about 25%) held in solution by forces which ordinarily govern solubility in salt solution. 2. A larger portion (about 50%) which remains in solution by virtue of the retarded precipitation that is characteristic of supersaturated solutions of calcium carbonate and phosphate, perhaps as the result of the presence of the parathyroid hormone. 3. A portion (about 25%) held in solution by the serum proteins (Peters and Van Slyke (13)). With protein breakdown as much as 2.5 mg. % calcium may be liberated. This may contribute to the frequency with which calculi are found in this and other similar debilitating diseases.

The role of hypoproteinemia in wound healing and wound disruption has been experimentally and clinically confirmed. The not infrequent instances of edematous stomata following gastro-enterostomies have received attention because of the obstructive symptoms they produce.

The importance of adequate plasma protein values for the prevention of liver damage and for the restoration of normal liver lipids in fatty livers has been carefully worked out by Ravdin and his coworkers (14, 15, 16, 17). Vulnerability of the liver to damage by anaesthetic agents and anoxic states has been emphasized by the same investigators. This group was among the first to teach that adequate protein administration was a more important element in liver protection than adequate carbohydrate supply, with the additional warning that plasma protein will not be replaced by the administration of a high protein diet unless there is in addition a carbohydrate supply adequate for caloric needs. Only after the caloric need is met will ingested or injected proteins be utilized to replace tissue and plasma proteins. When tissue proteins are depleted the administered proteins will be utilized to replace tissue proteins first; serum proteins may remain low over a period of time. Elman's (8) studies have shown that the proportion of tissue protein depletion to plasma protein is of the order of thirty to one, i. e., for every gram reduction demonstrated in plasma proteins there has been a thirty gram loss in tissue proteins. This must be borne in mind in calculating quantitative replacement.

Calculus Formation: The three cases reported in this paper all showed clinical calculus formation. Two of the cases showed both gall bladder and kidney

stones; one showed kidney stones. It is a summation of factors which is responsible for the formation of stones; the derangement including acceleration in both calcium mobilization and precipitation. Mobilization is increased by the decalcification of disuse seen in simple bed rest and demonstrated most dramatically in cast immobilization of fractured extremities. Secondly there is the release of calcium mentioned above in protein depletion. Thirdly in acidosis so frequently accompanying the debilitating gastro-intestinal diseases, bone decalcification is accelerated. Added to these sources of increased mobilization there is the factor of dehydration with increased concentration of body fluids which lead to precipitation of salts out of solution and the role played by Vitamin A deficiency in increased calcium precipitation.

The role of Vitamin A deficiency in urinary calculus formation has been demonstrated experimentally and clinically. Osborne and Nedal (9) and Van Leersum (10) have demonstrated urolithiasis induced in Vitamin A deficient rats. Higgins (11) has produced urinary calculi in Vitamin A deficient dogs. The stones produced consisted chiefly of calcium phosphate and carbonate. The widespread occurrence of urolithiasis in the orient is considered dependent upon Vitamin A deprivation. The mechanism appears to be related to the known effect of Vitamin A deficiency in impairing epithelial structures and in promoting keratinization. McCamson (12) believes that desquamated keratinized epithelium from the urinary organs may provide the nucleus about which crystalline material is deposited. Eusterman's case of gastro-jejuno-colic fistula resulted in Vitamin A deficiency and night blindness, but he does not report stones in this case.

Vitamin Deficiencies: Functional alteration in the small intestine due to Vitamin B deficiency in ulcerative colitis and other intestinal diseases associated with nutritional deficiencies have been described by Golden (6) and Mackie (5). Golden's description reads, "in the earlier less advanced stages the barium sulfate may pass rapidly through the jejunum reaching the lower part of the intestinal tract in a quarter of an hour and entering the caecum in less than a half hour . . . in the more advanced stages the movement of the barium sulfate is slowed. It may not reach the caecum in six hours or longer." He describes segmental puddling and retention of barium in the advanced stages. Ravdin points out that the roentgen appearance of the small intestine in dogs with experimental hypoproteinemia is indistinguishable from that of dogs with Vitamin B deficiency. It has been suggested that these alterations seen in hypoproteinemia may be due to a reduced "acceptance" of vitamin B by hypoproteinemic tissue.

As demonstrated in the appended case reports, the peripheral neuritis of Vitamin B deficiency may become so severe as to produce complete paralysis. The bilateral foot drop exhibited by this patient in the course of his illness is a dramatic example of this deficiency. It

should be mentioned that although this is obvious and easily demonstrable that other more subtle manifestations of Vitamin B deficiency exist and go unrecognized. Long before such complete paralysis occurs, milder symptoms such as heaviness of the lower extremities, calf muscle cramps, paraesthesias of the toes and fingers, burning of the feet and pain in the legs appear. Vibratory sensation may be lost in the toes. Ankle jerks are diminished or absent. Knee jerks may disappear and finally position sense of the toes becomes impaired. Calf muscle atrophy develops and foot drop follows. The medical complications of Vitamin B deficiency may be mentioned only in that a patient with ulcerative colitis and advanced Vitamin B deficiency constitutes a critical surgical risk if he shows evidence of an enlarged heart or a serous effusion and has had any history of circulatory collapse attributed to myocardial damage as the result of Vitamin B deficiency; the so called Beri-beri heart.

The underlying mechanism by which vitamins function is not completely understood. The slowing or halting of cellular metabolism resulting from their deficiencies is recognized. Vitamin B₁ is intimately concerned with the normal metabolism of carbohydrates. It acts as a carrier of oxygen and is necessary in the normal completion of carbohydrate oxidation. We may ply a Vitamin B₁ deficient patient with a high carbohydrate diet to meet his caloric needs and wonder why he fails to utilize it until his B₁ deficiency is overcome. Until B₁ deficiency is overcome the cells cannot utilize the carbohydrate offered, the caloric needs will not be met and administered proteins may fail to achieve cellular or plasma replacement.

Vitamin A: Wilbur and Eusterman (18) report a case of night blindness in a patient with a gastrocolic fistula. Night blindness is due to a delay or failure of regeneration of visual purple in the retina which is in turn due to Vitamin A deficiency. Repair of the fistula resulted in complete recovery from the night blindness. The role of Vitamin A deficiency in calculus formation has been mentioned above.

Hormonal Deficiency: Infantilism due to glandular hypofunction in nutritional deficiency states appears infrequently in the literature. It is described by Alpert (19) in a seventeen year old diabetic who before the insulin era was treated by a starvation diet; she showed advanced evidence of physical and sexual immaturity. One year after insulin became available, normal physical and sexual maturity were obtained. Langston (20) reports a seventeen year old boy with congenital hemolytic icterus, whose development was that of an eleven year old child. Splenectomy followed by anterior pituitary extract resulted in a dramatic development to normal physical stature. Benson and Barger (21) reported a series of twelve cases of retarded sexual and somatic development occurring in ulcerative colitis. Davidson (22) has reported three cases of ulcerative colitis from the medical service at Montefiore Hospital. Two of Davidson's three cases came to autopsy. Each

showed that there was basophilic hyperplasia of the pituitary similar to that seen in Vitamin A and E deficient rats. In animals it implies a compensatory reaction to partial castration. In the human it may be interpreted as a secondary pituitary response to a sub-functioning testes. The pathological reports on the sex organs were identical in both cases. They read, "The testicles in each case were small and prepubertal. The tubules were small. There were no mitotic figures or any evidence of maturation. The interstitial cells were swollen with round vesicular nuclei and colorless cytoplasm."

In the case presented tonight the patient was nineteen years old, showed all the signs of pluriglandular infantilism in the absence of breasts, absence of pubic hair and epiphyseal markings of a child of twelve. These pluriglandular manifestations represent evidences of hypofunction for which we have no laboratory tests. These glands reflect their metabolic derangement in alterations in physiological function resulting in the younger age group in an underdevelopment such as described above.

Hemoglobin and red cell formation: Ordinarily the restoration of hemoglobin and red blood cells is associated with iron ingestion or injection of liver extract or transfusions. It should be remembered that red cell formation requires proteins and in hypoproteinemic states red cell regeneration is markedly retarded. When anemia and hypoproteinemia coexist, hemoglobin production has precedence over plasma protein production (Robschheit-Robbins (23)).

In nutritional deficiencies such as indicated above, replacement pre-operatively in a surgical case or as a main course of treatment in a medical case depends upon the ability of the intestinal tract to accept and absorb adequate diets. In any attempt to replace proteins it has been pointed out by Ravdin (14, 15, 16, 17) and others that unless an adequate caloric requirement in the form of carbohydrate is administered, protein will be utilized for energy rather than for replacement. Many of the failures in protein alimentation have arisen from this error in dietary management. No protein will be stored until the energy requirements have been fulfilled. Ravdin suggests a diet consisting of 75% carbohydrates, 20% protein and 5% fat in preparation for surgery in patients who are either obviously hypoproteinemic or in patients with gall bladder disease with increased lipids in the liver.

Elman (8) suggests milk, skim milk, eggs, lean meat and soy beans as excellent sources of protein when these can be administered by the oral route. Where

protein nourishment is difficult as it is in cases of ulcerative colitis there has been developed preparations of amino acids containing casein hydrolysates which can be taken by mouth or intravenously. In chronic hypoproteinemia due to malnutrition plasma transfusion which is of such inestimable value in acute protein deficiencies in hemorrhage, shock or burn may be a disappointment. This is to be expected since the plasma protein values represent only a measuring stick of body protein depletion and replacement. Each gram loss of plasma protein represents a 30 gm. loss in tissue protein. The replacement therefore requires a quantity of protein which would be impractical to supply through plasma transfusions. Hydrolyzed protein can be administered intravenously in 5% solution with 5% glucose. Such a solution supplies 50 grams of protein per 1000 cc. In preparing nutritionally depleted patients for surgery some form of hydrolyzed amino acids should be added to the glucose and salt infusions. If the intestinal tract is available, one may administer by mouth 250 gms. of Amino Acids and 500 gms. of carbohydrate every twenty-four hours. If this is not tolerated, 500 gms. of dried milk per day will furnish 25 gms. of Nitrogen.

For already existing vitamin deficiency Jolliffe (24) advises erring on the side of wasting the vitamin by massive dosage rather than giving a suboptimal amount. He suggests that vitamin supplements in addition to an adequate diet should include Vitamin A, 50,000 international units, ascorbic acid, 400-500 mg., Thiamine Chloride, 300-1000 mg., the first day and a maintenance of 50-200 mg. each day along with a source of the entire B complex included in Vegex, 20 gms. Brewer's yeast, 60 gms., aqueous liver extract, 30 grams. Starr (25) adds riboflavine, 10 mg., nicotinic acid, 100 mg., Vitamin K, 2 mg. (in hemorrhagic states due to prothrombin deficiency).

In these disease states the functional derangements are widespread. The underlying mechanisms are multiple. The signs and symptoms are diffusely distributed throughout the body as demonstrated in night blindness and foot drop. Yet the principles involved in their control are few. Rehydration, remineralization, protein and vitamin replacement and finally surgical removal of the organic etiological agent.

Proper preparation is disappointingly slow and often incomplete as demonstrated in the cases presented. Yet any improvement makes surgery less hazardous. When the organic disease is removed the focus for reflex dysfunction of the organically uninvolved intestine is eliminated and the intrinsic compensatory mechanisms swiftly restore the constancy of the deranged internal environment to normal values.

REFERENCES

1. Ochsner, A. and DeBakey, M.: Arch. Surg., 40:208, 1940.
2. Idem.: J. A. M. A., 114:117, 1940.
3. Volpito, P. P. and Risteen, W. A.: Anaesthesiology, 4:403, July 1943.
4. Mackie, T. T.: Med. Cl. N. A., 17:165, July 1933.
5. Mackie, T. T.: J. A. M. A., 117:910, Sept. 13, 1941.
6. Golden, R. J. A. M. A., 117:913, Sept. 13, 1941.
7. Prendergrass, E. P. et al: Radiology, 26:651, June 1936.
8. Elman, R.: Med. Clin. N. A., March 1943.
9. Osborne, T. B. and Nedel, L. B.: J. A. M. A., 69:32, 1917.
10. Van Leersum, E. C.: J. Biol. Chem., 76:137, 1928.
11. Higgins, C. C.: Jour. of Urology, 36:168, 1936.

12. McCamson, R.: Brit. Med. J., 1:717, 1927.
13. Peters and Van Slyke: Quant. Clin. Chem., Williams and Wilkins, Vol. I, p. 810, 1931.
14. Ravdin, et al: J. A. M. A., 121:322, Jan. 30, 1943.
15. Ravdin, et al: J. A. M. A., 114:107, Jan. 13, 1940.
16. Ravdin, et al: Ann. Surg., 114:1018, Dec. 1941.
17. Ravdin, et al: S. G. O., 66:812, May 1938.
18. Wilbur, D. L. and Eusterman, G. B.: J. A. M. A., 102:364, Feb. 3, 1934.

19. Alpert, E., Translated by R. W. B. Ellis, London, M. Hopkinson, 1933.
20. Langston, W. Smith: Med. J., 28:316, 1935.
21. Benson, R. E. and Borgen, J. A.: Gastroenterology, 1:147, Feb. 1943.
22. Davidson, S.: Arch. Int. Med., 64:1187, Dec. 1939.
23. Robscheit-Robbins, F. S.: Federation Proc., 1:219, 1942.
24. Jolliffe, N.: Bull. N. Y. Acad. Med., July, 1934, p. 469.
25. Starr, P.: Int. Abstr. Surg., 74:309, April 1942.

DISCUSSION BY DR. ARTHUR M. WRIGHT

The cases presented and the paper read this evening are both examples of the changing thought in surgical practice and surgical teaching. These are presented as physiological derangements with surgical technique as a method in our therapeutic armamentarium. Surgery was merely a means to an end. There was no stress laid on the technique required, the suture material used or a new clamp for a special purpose. The paper deals with fundamental concepts rather than with isolated details.

There was a time when a student was taught the detailed symptoms of a disease which he then had to label with a name. He was then taught to treat this label. His excellence as a student was then measured by the number of such labels he could conjure up out of his memory. Teaching today stresses the underlying physiological derangements responsible for the symptoms seen in the disease. The student thus becomes rich in principle rather than in fact. He learns to bring together under one common denominator various diseases that have no apparent clinical similarity but which share a common physiological dislocation.

An example of the advantage of this type of understanding of disease was illustrated in the cases presented. One need only have a student understand that hypoproteinemia occurs in a disease and the reason for its occurrence. He knows all of the symptomatology that follows hypoproteinemia no matter how induced. He thus realizes the oneness of the origin of symptomatology. The principles responsible for the symptomatology hold universally without regard to the body system involved.

In this paper it is demonstrated that the autonomically innervated gastrointestinal tract induces remote reflex functional derangements in response to organic disease similar to those found with thrombo-phlebitis or arterial thrombosis in the vascular system.

The training of a surgeon has changed within the relatively recent past. Perhaps it is more an amplification than a change. There was a time when the professor of surgery had held a similar position in anatomy and a training in anatomy was considered the most important apprenticeship to surgery. The need of a knowledge of altered anatomy in disease states led to the additional training in pathology. Today the need to understand the functional alterations associated with anatomical disease brings the next preclinical science to the foreground in the training of a surgeon. The physiologist is now taking his place alongside the anatomist and the pathologist, establishing the truth of Harvey Cushing's definition of a surgeon. He speaks of him as "that medically trained artisan we call a surgeon."

CASE I — W. S., born 1907.

In May of 1939, at the age of thirty-two, he was admitted to another hospital in the city with a history of mucous diarrhea, weight loss, fatigue and abdominal pain. He had a history of having had frequent bowel movements for some ten years previously. He had never noticed gross blood in the stool. His recent weight loss was twenty pounds.

At that hospital he showed an anemia of 2.9 million red cells and 50% Hgb. His stool was negative for amoeba, typhoid, dysentery group or tuberculosis. It was Benzidine positive.

In July, 1939, at that hospital he had a polyp removed from the rectum, and a double barrel ileostomy performed for an established diagnosis of ulcerative colitis. He showed some improvement, gained weight, and felt generally better following this procedure.

In October, 1939, he had a history suggesting left nephrolithiasis which subsided spontaneously.

In April, 1940, he was readmitted to the hospital for a perirectal abscess at the site of the removal of the rectal polyp which had never healed. This was incised and drained but failed to heal. This anal lesion continued with advancing severity throughout his illness.

After this brief improvement his symptoms returned with increasing severity. He lost weight and strength and on October 7, 1940, was admitted to Montefiore Hospital bedridden, complaining of exquisite pain in the anus and abdominal cramps. He had become an addict demanding morphine for relief and requiring one quarter grain of morphine six times a day for relief.

Physical examination revealed a cachectic male (Fig. 1A). (weight seventy-eight pounds from an original weight at the start of his illness of one hundred and forty-nine) psychically demoralized, a beefy red tongue and ulcerations at the angles of the mouth, characteristic of advanced vitamin B deficiency. He had a draining ileostomy, with an adjacent abdominal wall abscess, a sloughing perineum, an anal region in which the terminal anus had sloughed away with the rectal opening in the hollow of the sacrum some two inches above the skin margin. There was a profuse bloody purulent discharge from the rectal stoma.

Laboratory data showed a profound anemia: 2.9 M. Hgb. 53%. His blood urea was 10.7 mgm. %. His white blood count varied from twelve to twenty thousand with a high poly differential. His total protein varied between four and five grams % with no A. G. reversal. He did not develop nutritional edema.

He was put on a high caloric, high vitamin diet with repeated transfusions and infusions of glucose and saline. Massive vitamin therapy was tried giving the whole vitamin B complex with riboflavin and nicotinic acid. For a time he received 50 mgm. of nicotinic acid every hour for ten hours a day for a period of five days. Chemotherapy was given in the form of sulfaguanidine through the distal ileostomy loop. The patient showed little improvement under this treatment.

On May 12, 1941, the first stage colectomy was performed through a transverse incision. The colon was removed from the ileum to the sigmoid (Fig. 2). The distal sigmoid being left out on the abdominal wall as a mucous fistula. His post-operative course was stormy for the first week. He then began to show slow improvement.

On November 3, 1941, the perineal sloughing wound measured some six inches by three inches in diameter and the terminal rectum was at the apex of this wound draining a bloody purulent discharge.

On November 11, 1941, an abdomen-perineal resection was performed removing the remainder of the involved colon.

On June 22, 1942, the patient had an attack of calculous cholecystitis with jaundice which subsided spontaneously.

In May, 1942, a skin graft to the perineum failed to take, and the wound was permitted to granulate in spontaneously.

On November 18, 1942, all wounds had healed. The



Fig. I, Case 1 — A. November, 1941, one week after complete colectomy. Weight 85 pounds (preoperative weight 70 pounds).
B. November, 1942, one year after colectomy. Weight 154 pounds.
C. Demonstrates 3" protruding ileostomy which falls into bag and spares skin irritation of ileal contents.



Fig. II, Case 1 — Colon from terminal ileum to sigmoid; first stage of colectomy. Note complete mucosal destruction with pseudo-polyps.

patient had gained seventy pounds in weight back to his original one hundred and forty-eight pounds (Fig. 1B and C). He was left with a draining ileostomy for which he wears a bag and was discharged from the hospital on November 21, 1942.

This case is presented as one of advanced ulcerative colitis which failed to respond to medical treatment and did not show significant improvement until the entire colon was removed. Colectomy was followed by prompt and progressive improvement. Except for the unavoidable ileostomy the patient's physical health has been restored almost to its original state.

This case is presented as one of advanced ulcerative colitis which failed to respond to medical treatment or ileostomy and which showed functional recovery following removal of the organic pathology by complete colectomy. He demonstrates a nutritional deficiency with clinical urinary and gall bladder stones. Neither of these were proven surgically.

CASE II — K. S., born 1920.

In March, 1937, at the age of 17, the patient was admitted to a hospital in New York with a diagnosis of subacute appendicitis. She had been a "sickly" child for several years before but had had no acute illness. Her complaints at that time were abdominal pain, some diarrhea and vomiting. She had been menstruating scantily for three years. Menstruation stopped at this time and has not returned. Laparotomy at this time revealed a diffuse intestinal tuberculosis. A section of omentum and a lymph gland were removed at this time,

both of which were pathologically demonstrated as being tuberculous. No further surgery was done at this time. Ten days later the patient was reopened and an ileo-transverse colostomy was performed on the right side of the transverse colon. Following this operation she developed multiple abdominal fecal fistulae which persisted. Her symptoms of diarrhea, abdominal pain and occasional distension and vomiting continued. A chest plate at this time showed a minimal, inactive tuberculosis of the left upper lobe. She was sent to a sanatorium for treatment for six months. The x-ray appearance of this lesion has not changed and has remained quiescent through these years.

On April 26, 1940, eighty centimeters of small intestine were resected and an ileotransverse colostomy performed at the distal end of the transverse colon. The ileal stump entering the caecum was closed thus sidetracking the ileum, caecum and adjacent colon and the fistulae leading from them to the intestinal wall. The post-operative course was stormy for two weeks, requiring multiple transfusions and infusions to maintain water balance. Macroscopic examination and microscopic examination of the removed specimen were reported as showing tuberculosis. A lymph node attached to the specimen showed typical tubercles and areas of caseation.

Following this procedure the abdominal wall inflam-

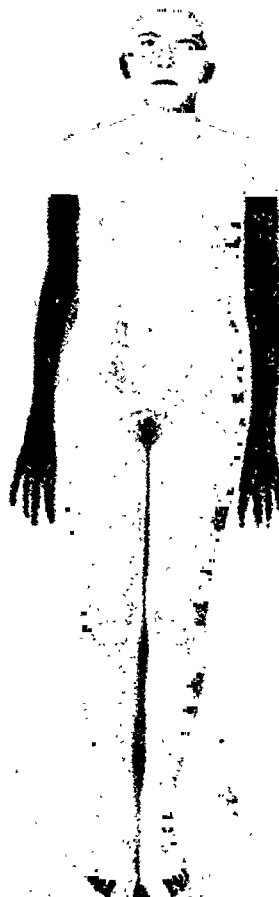
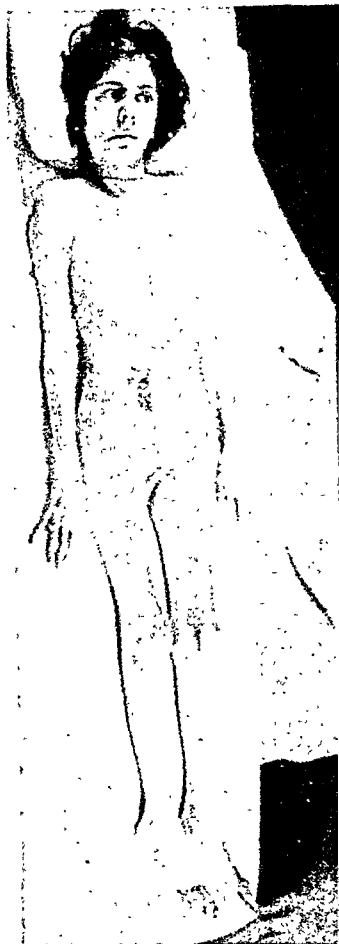


Fig. III, Case 2 — A. April, 1940, before operation, weight 50 pounds. Note absent breasts and pubic hair of infantilism. Age 19, appeared to be 12-13 years old.

B. November, 1940, eight months postoperative. Weight 104 pounds. Note development of breasts and pubic hair, general maturity of face and body.

On January 17, 1938, she was admitted to Montefiore Hospital. She was bedridden, emaciated, weighed fifty pounds, showed all the signs of pluriglandular infantilism (Fig. III) with absence of breasts and pubic hair. Her epiphyseal markings were those of a child of twelve (Figs. IV and V). Her abdomen showed multiple fecal fistulae draining small intestinal contents. A note by the physio-therapy department at this time remarked "The patient is learning to walk." She showed carious degenerated teeth (Fig. VI).

In March of 1940 she was seen by the surgical service and since the pulmonary disease was considered minimal and inactive and the patient was a hopeless invalid with the abdominal pathology that existed, surgery was decided upon.

mation subsided with the reduction in fecal flow and on March 17, 1941, a resection of the terminal ileum, caecum, ascending colon and transverse colon to the distal ileo-transverse colostomy was performed. The abdominal wall containing the fecal fistulae was removed in one mass with the intestine. The post-operative course was smooth following this procedure. The pathological report on this specimen which had been exposed to infection by the fecal fistula was reported as nonspecific granuloma of the intestine.

Before going to the surgical service she was treated by diet, iron, vitamins, cortate, estrogenic substances, pituitary and ovarian products, liver extracts and multiple transfusions but showed no improvement on this care. Following the second procedure improvement was pro-

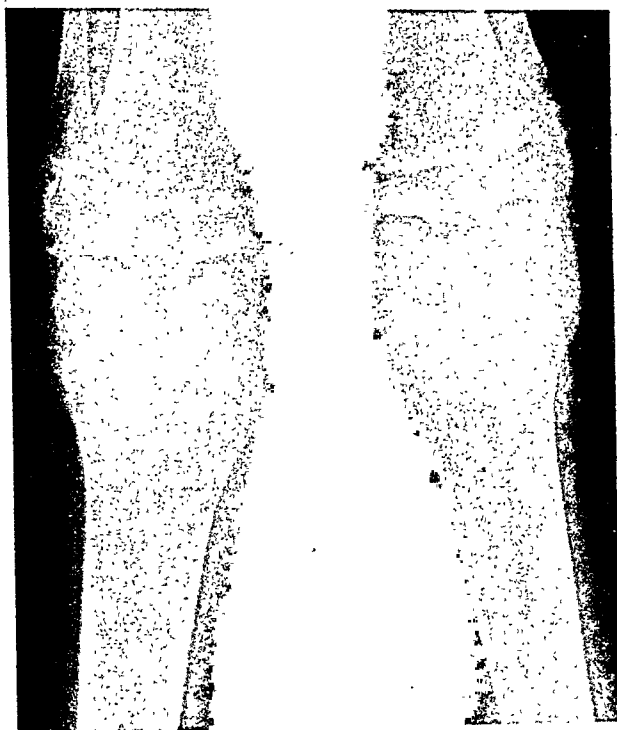


Fig. IV, Case 2 — A. Anteroposterior view showing epiphyses of child of 12 (patient 19 years old) March, 1938.

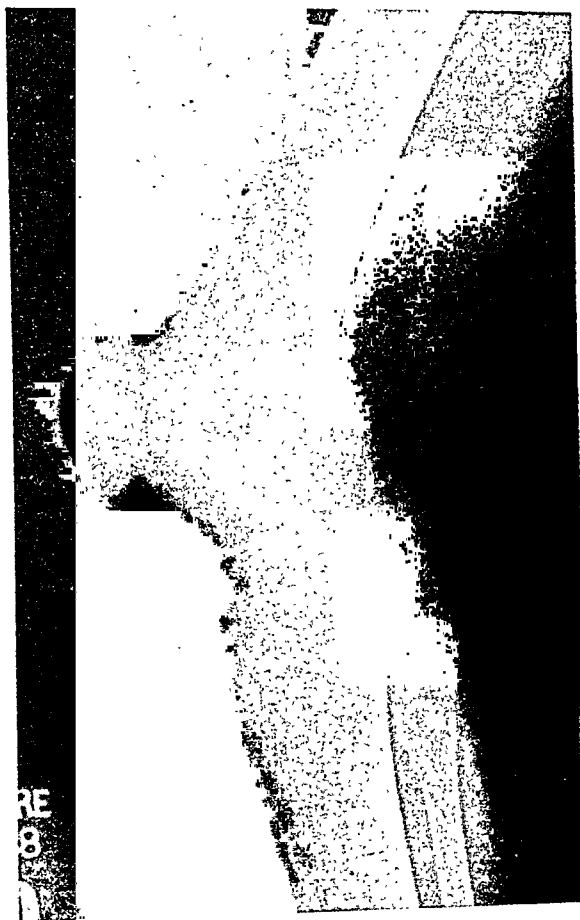


Fig. V, Case 2 — A. Lateral view showing epiphyses of child of 12 (patient 19 years old) March, 1938.



Fig. IV, Case 2 — B. Showing adult fused epiphyses December, 1943.

gressive and eight months after the second procedure her weight had risen to one hundred and four pounds (a gain of fifty pounds). There was obvious disappearance of the signs of infantilism. Pubic hair reappeared, breast development was noted (Fig. IIIB) and except for an occasional diarrheal stool patient had no complaints.

This patient developed calculi in both the kidney and the gall bladder. In June, 1940 (between the first and second intestinal operations), the patient developed an obstructive infection in the right kidney for which a pyelolithotomy was performed. In August of 1943 the patient developed an acute obstructive calculous cholecystitis for which a cholecystostomy was performed with removal of stones.

This patient is presented as a case of nutritional deficiency showing:

1. Pluriglandular infantilism and
2. Proven calculous formation in the kidney and the gall bladder.
3. Functional recovery following complete removal of the organic pathology.

CASE III — A. K., born 1910.

Oct., 1938. Onset at the age of 28 with abdominal cramps, diarrhea, blood and pus in stools. Weakness, loss of appetite, weight loss and fever.

Jan., 1939. Admitted to a hospital where x-ray and sigmoidoscopy showed the lesion of ulcerative colitis. Ileostomy was performed with no improvement. Weight loss from 215 to 145 (70 pounds). Anemia with haemoglobin of 44% and one report of 25%.



Fig. V, Case 2 — B. Showing adult fused epiphyses, December, 1943.

Aug., 1939. Admitted to Montefiore Hospital on the Medical Service, where despite high protein diet, infusions, transfusions, whole yeast, thiamin chloride 100-200 mg. a day, nicotinic acid 500 mg. a day, iron, cortate,



Fig. VI, Case 2—Degenerated upper teeth due to nutritional deficiency.

riboflavin, sulfanilylguanidine, and local care, the patient showed progressive deterioration.

May 11, 1940. First seen by Surgical Service. Examination showed marked evidence of weight loss despite a diffuse edema of legs and trunk due to hypoproteinemia of 3.7 gms. % with a reversed albumin globulin ratio, A/G ratio being 1.5/2.2. An anemia showing an hgb. of

7.5 gms. (normal 17 gms.) and red blood count of 3.3 million.

Advanced evidence of vitamin B deficiency despite vigorous treatment was seen in loss of vibratory sense, absent ankle jerks and bilateral foot drop so patient was unable to walk, exquisite tenderness and calf atrophy. Feet had been immobilized in molded plaster splints to escape contractures due to foot drop.

Abdominal examination showed a draining ileostomy with multiple intestinal fistulae about the ileostomy and multiple peri-anal fistulae from rectal lesion. X-ray and sigmoidoscopy showed involvement of entire colon and rectum.

May 23, 1940. First stage of colectomy was done through a transverse incision through which the colon from terminal ileum to sigmoid was removed (Fig. VII), leaving the distal sigmoid out of the wound. The first post-operative week was a stormy one. Fluid balance was preserved with infusions and transfusions.

Improvement was slow but progressive. Weight rose to 182 pounds (some 40 pounds gain). Total protein rose to 7.7 gms. % with an A/G ratio of 4.5/3.2 and edema disappeared. All the signs of vitamin B deficiency disappeared foot drop was relieved and patient was able to walk. Hgb. rose to 88%.

A year was allowed to elapse, but pus and blood continued to be discharged by rectum and sigmoidostomy, the perianal fistulae remained uncontrolled and there were recurrent bouts of fever. Sigmoidoscopy showed involvement to anus.

May 1, 1941. A one stage combined abdomino-perineal resection was done removing the remaining colon and rectum. Recovery from this was uneventful. The wounds



Fig. VII, Case 3 — Colon from terminal ileum to sigmoid; first stage of colectomy. Note mucosal destruction.

healed well, the perineal wound continued to have a slight, but foul discharge. The ileostomy functioned well, semi-solid fecal material discharged from it. A prolapse of four inches let it fall into the bag sparing the skin from erosion.

Nov. 5, 1941. Because prolapse has become six inches

long, this was revised and mesentery sutured to prevent prolapse. At the same time the posterior wound was reopened and packed with sulfathiazol.

Dec., 1943. Patient has a blood count of 4.3 million, Hgb. 88%, normal total protein and A/G ratio, now weighs 215 pounds, is in good health.

The pathology was reported as granuloma of colon at first resection and ulcerative colitis in the second. In January, 1939, at another hospital the patient had hematuria and cystoscopy at that time revealed a hemorrhagic cystitis, biopsy of which was reported as chronic granulation tissue.

In January, 1940, at Montefiore Hospital the patient developed an attack of left renal colic with typical pain distribution and hematuria. On February 16, 1940, he passed a 2 mm. yellow brown calculus in the urine.

This patient is presented as showing a nutritional deficiency due to ulcerative colitis which resulted in:

1. Peripheral neuritis with foot drop due to Vitamin B deficiency.
2. Massive oedema due to hypoproteinemia, and
3. Proven urinary calculus.
4. Complete recovery followed removal of the organic pathology.

Proctalgias and Allied Non-Inflammatory Perianal Dyscrasias: Coccygodynia Proctalgia Fugax, Neurogenic Pruritus Ani.

By

EMIL GRANET, M.D.

NEW YORK, N. Y.

THE ANO-RECTAL SYNDROMES to be discussed are not infrequently seen in practice and are of interest because each poses problems in etiology, pathological physiology and treatment, the satisfactory solution of which in most cases eludes us. Commonly, pain or discomfort in the perianal region or rectum is due to conditions associated with inflammation or infection. These lesions include:

1. Acute Abscesses — Perianal, Perirectal, Ischio-rectal, Supra-levator, Cryptitis, Pilonidal
2. Fistulae
3. Acute and Chronic Fissures
4. Acute Thrombotic Hemorrhoids
5. Specific Chronic Infection — Perianal Tuberculosis, Gonorrhea, Syphilis, Lymphogranuloma Venereum
6. Ulcerative Colitis — Idiopathic, Dysenteric, Amebic, Chronic Hypertrophic Proctitis.

Neoplasms, benign or malignant, involving the anus, rectum, or pelvis, are obvious causes of perianal pain or discomfort.

COCYGYDYNIA

The pain in this syndrome centers about the coccyx, frequently radiating up the rectum, laterally to the gluteal region, and occasionally down the back of the thighs. The characteristic pain is severe, continuous, throbbing, and is commonly brought on by prolonged sitting. Trauma resulting from falls on the sacro-coccygeal region or following parturition, or even after ano-rectal surgery is considered the chief etiologic factor of onset in this syndrome. Lesions of the coccyx itself following trauma are infrequent as demonstrated by Duncan (1). He found that in patients with coccygodynia studied at the New York Orthopedic Hospital, fracture of the coccyx was found in only 4% and dislocation in 2% of 262 patients.

The usual symptomatic treatment with sedation, physical therapy, strapping, injection of analgesics about the coccyx, and even coccygectomy have too frequently given little or no relief to the patient. Thiele (2) as a result of careful observation over a period of years believes that the pain in this condition results from tonic spasm of the pelvic muscles which insert into the lateral margins of the coccyx. He reports that as early as 1859, Sir J. Y. Simpson described this mechanism by calling attention to the fact that, "when the coccyx or the coccygeal joints have been injured, or when the surrounding tissues were the seat of inflammation, any contraction of the muscles attached to the coccyx would excite the characteristic pain of coccygodynia." Thiele demonstrated the definite relationship between the syndrome of coccygodynia and tonic spasm of the levator ani and coccygeal muscles, and in some cases of the piriformis. In 53 patients with coccygodynia personally treated by this author, the physical findings were described as follows: "On digital rectal examination with the patient in the Sims' position, spasm of the levator and coccygeus is easily detected by latero-posterior pressure, the spastic muscles being felt stretched from their origin at the arcus tendineus or ischial spine to the side of the coccyx and the lower part of the sacrum." Piriformis spasm is difficult to detect because the distance of this muscle from the anus makes palpation uncertain.

My personal experience with 12 patients from the Proctological Clinic at the New York Hospital and 8 patients seen in the naval service afloat and ashore, all of whom suffered with coccygeal pain, completely confirms Thiele's findings. However, an added finding, to my knowledge not previously described, was found in about half of the cases seen. This was the presence of well-developed bursae which on finger palpation were found in the lateral pelvis situated between the pubo-coccygeus and the ileo-coccygeus portions of the levator

ani. These averaged about 1.5 x 3 cm. in size, were flat, oval, crepitant, and during the acute phase, were exquisitely tender. It is readily conceivable that levator-coccygeus bursitis resulting from injury or infection can cause coccygodynia.

The definitive treatment of coccygodynia is directed toward alleviating muscle spasm. The technic originally described by Thiele places the patient on the table in the Sims' position with the operator's cotted finger inserted full length into the rectum. He continues — "Latero-posterior pressure will place its flexor surface horizontally across the surfaces of the levator ani and coccygeus muscles almost at a right angle to their fibers. These muscles are massaged in the long direction of their fibers in the same manner that a strop is stroked by a razor. Massage is begun lightly. This is necessary because one does not wish to traumatize the extremely tender spastic muscles. As the patient makes subsequent visits, massage is made with increasing pressure. If definite improvement does not result after the first four to six massages over a period of a week or ten days, orthopedic consultation should be sought." My patients were treated every other day for two weeks, then twice weekly for two weeks, and continued at this rate until symptom free. If no improvement was obtained after six treatments, the case was considered a therapeutic failure for this method. Of these, 66% were cured, 30% improved, and 4% or 2 patients were unimproved. My own experience with this method fully confirmed Thiele's good results with massage treatment. Those with tender inflamed bursae did well on massage, the size and tenderness of the bursae subsiding with clinical improvement.

In brief, the syndrome of coccygodynia is associated with tonic spasm of the para-coccygeal muscles and in some instances, with related bursitis. These conditions were commonly cured or alleviated by repeated finger massage of the para-coccygeal muscles, the aim of which is directed toward relieving pain-producing spasm.

PROCTALGIA FUGAX

This term introduced by Thaysen (3), describes a syndrome of idiopathic rectal pain of not infrequent occurrence. The clinical picture varies in individuals but a typical case can be described as follows:

Onset is insidious, without warning, often awakening the patient from a sound sleep in the early hours of the morning. The patient is aware of a sense of discomfort in the rectum, localized some 5-10 cm. above the anus, which increases rapidly in intensity to a point associated with mild shock, or even unconsciousness. In its most severe form, it is described as an agonizing localized pain as if "caused by an expanding balloon." The paroxysm persists at maximum intensity for some 5 to 10 minutes, then gradually subsides, leaving the patient with a feeling of marked weakness and fatigue. With the resulting relief, the sufferer speedily falls asleep. The anus itself is not primarily involved al-

though secondary voluntary spastic muscular contractions are common. Voluntary attempts by patients to relieve themselves of intra-rectal pressure are instituted, such as attempts to pass gas, or defecate, by hot baths, enemata, and various changes of position. These measures have little effect on the condition. The actual cause of the pain is not known. No definite relationship to rectal inflammatory or other pathological lesions have been described. Bolen (4) had the opportunity of examining a patient during the occurrence of an attack. Inspection through the sigmoidoscope showed an injected rectal mucosa with edema and prominence of the blood vessels. The recto-sigmoidal junction was closed and apparently in spasm. As the instrument advanced through the spastic lumen, the patient passed considerable flatus, and relief of pain ensued. Above the recto-sigmoidal juncture, sigmoidal mucosa presented a normal appearance.

Most reports state that individual attacks occur one to three times a year. The infrequency of the attacks and their almost universal occurrence in the night make vigorous therapy ill-advised and difficult to evaluate. The unpredictable onset and infrequency of the attacks make prophylactic measures impossible to administer. Its probable psychosomatic nature is suggested by its onset in sleep, often during periods of tension states (fear, guilt, fatigue), and its onset in various reports following coitus, masturbation, and other phases of exciting sexual states.

Inasmuch as spasm in the region of the recto-sigmoidal juncture is probably the actual pain-producing mechanism, its alleviation by a promptly acting anti-spasmodic medicament is indicated. Patients with idiopathic spastic rectal pain should be provided with either ampules of amyl nitrite or tablets of glyceryl trinitrite for rapid smooth muscle relaxation when in the symptomatic state.

NEUROGENIC PRURITUS ANI

Intolerable itch at the anus, pruritus ani, is extremely prevalent. The etiologic factors in most of these patients can be determined by diligent and painstaking investigation. Among these are the allergies, parasitic infestation, the mycoses, and in many cases, specific sensitivity of the perianal skin to chemical irritants in the feces, Granet (5). Furthermore, anal pruritus can be caused by irritating secretions having origin in obvious anal or perianal pathological lesions such as fistulae, fissures, ulcerated prolapsing hemorrhoids, and verrucae. These patients are easily cured by corrective surgical therapy.

The perianal skin in chronic pruritus ani exhibits various degrees of inflammatory reaction starting with the early eczematoid rubor to culminate after many years in the thickened, rugated "dead white," moist degenerated epidermis, characteristic of extremely persistent cases. Dependent on the etiology in the individual case, proper therapy conscientiously adminis-

tered and utilized indefinitely by the patient will afford relief, if not cure, in most of these patients.

The occasional case with persistent anal pruritus remains, in which no known etiological factor can be demonstrated, despite our most painstaking investigations. These patients continue persistently symptomatic, despite empiric utilization of the gamut of our therapeutic armamentarium. Furthermore, despite constant pruritus, the perianal skin of these patients shows no signs of the usual chronic dermatitis or thickening, though it may present evidence of self-induced scratch marks. Except for these, the perianal skin of these patients is essentially normal in all respects. Three such patients occurred in a series of 100 patients personally studied. These were women with definite personality difficulties, all of whom had anal pruritus of long standing, with little or no perianal dermatitis, and who remained persistently recalcitrant to a routine of therapy which proved highly successful in allaying symptoms in most other patients in the series. The patient with persistent anal pruritus with no demonstrable etiology, and with relatively normal perianal skin, who in addition has personality difficulties or neurotic conflicts must of necessity be classified as a patient with neurogenic pruritus ani. That this type of individual is not rare is demonstrated by the fact that numerous reports of this psychosomatic disturbance have been published in current literature. It becomes increasingly clear that in certain neurotic individuals the anal pruritus may be the manifest subjective symptom derived in each case from hidden subconscious tension states. The definite pleasure relationship of pruritus ani and the scratching thereof is brought out by Drueck (6), who writes, "The occurrence of itching in an apparently healthy skin, as an expression of 'fixation phenomenon' arising from a submerged or repressed anxiety or desire, is familiar to both dermatologists and neurologists. The substitution of the pleasure of scratching an itching dermatitis for the pleasure of sexual orgasm is described by Sack (7) as 'organistic pruitique,' the patient creating the itch in his own mind, so to speak, in order to have the pleasure of gratifying his sexual desire by scratching it, perhaps without any dermatic foundation." Stokes (8) cites the case of an elderly gentleman who refused treatment of his ringworm with the frank remark that it resulted in more pleasant sensations than sexual relations with his wife. Stokes comments, "In this naive statement rests a great deal of truth, since it points clearly to the masturbatory element in many cases of pruritus, while the 'masochistic' element is inherent in the concomitant suffering and pain."

Rosenbaum (9) reports two cases of neurogenic pruritus perinei and concludes that "It is well known that the sensation of itching with its resulting scratching may result in pleasant and sensuous sensations at times actually resulting in sexual orgasm, while at other times (or at the same time) these symptoms may produce in-

tense suffering with violent scratching so that the end result almost amounts to complete self-destruction ('tearing oneself to pieces')."

Ferenczi (10) writes that a patient with an almost intolerable anal pruritus followed by irresistible tendency to anal and rectal masturbation showed no signs of symptomatic improvement in spite of a tedious investigation by means of associations. It was only after he had gone through a prolonged voluntary retention experiment and had eliminated the associated feelings of tension in the rectum as a pleasure-organ that the tendency to displace erotism to the genitalia became manifest.

Saul (11) describes the case of a young man who complained of occasional severe attacks of severe pruritus ani. In analysis, it became evident that the pruritus developed regularly on occasions when he would be taken out, for example, for dinner, by older men who were personally interested in him. The analytic material showed clearly that passive anal homosexual wishes were aroused by these situations. The patient gave a history of having indulged in homosexual practices in childhood with attempts at both active and passive roles. He occasionally indulged in anal masturbation and stated that he often used the pruritus merely as an excuse for this indulgence. Saul writes of a female patient who demonstrated a direct relationship between pruritus ani and passive homosexual wishes. The itching provoked insertion of the finger into the rectum and violent rubbing manipulation, which constituted an unrecognized form of anal masturbation. Her pruritus disappeared as satisfactory genital erotism developed.

Instances of the psychosomatic nature of idiopathic pruritus ani are becoming increasingly evident and for this reason, the related literature was quoted in detail. In practice we must recognize and suspect such cases. Local therapy is futile in such patients, and much time would be saved by psychotherapy utilized early in the disease.

SUMMARY

Several syndromes not of neoplastic or inflammatory origin, each of which causes pain or other discomfort in the perineal, anal, or rectal regions are presented as to etiology, pathological physiology and management.

The relationship of coccygodynia to spastic contraction of the muscles attached to the coccyx, and in some instances to a bursitis involving these muscles is discussed. Simple treatment by massage of the spastic muscles according to the method of Thiele results in rapid relief of pain with ensuing muscle relaxation.

The syndrome described as Proctalgia Fugax is difficult to study. Attacks of pain are sudden, occurring frequently with no prodromal symptoms and awakening the patient out of sleep. Severe spasm in the region of the recto-sigmoidal junction is suggested as the cause of the pain, and its psychosomatic nature seems well-established. Glyceryl trinitrite or similar rapidly acting antispasmodics may prove effective in therapy.

Chronic recurrent anal pruritus occurring in individuals with definitely established personality difficulties, the perianal skin of whom retains its relatively normal characteristics must be classified as neurogenic in origin. In these patients all local therapy affords no relief of symptoms. In the recent literature, numerous reports by both psychiatrists and dermatologists are quoted to demonstrate the "pleasure-pain" principle and its re-

lationship to pruritus. The masturbatory element is illustrated by the mechanism of rubbing or scratching while the masochistic element is inherent in the concomitant suffering. Cases of neurogenic pruritus are not obscure, must be recognized early and adequate psychotherapy instituted. Local treatment is futile in these patients.

REFERENCES

1. Duncan, G. A.: Painful Coccyx. Arch. Surg., 34:1088, 1937.
2. Thiele, G. H.: Coccygodynia and Pain in the Superior Gluteal Region. J. A. M. A., 109:1271, 1937.
3. Thaysen, T. E. H.: Proctalgia Fugax. Lancet, 2:243, 1935.
4. Bolen, H. L.: Spasmodic Rectal Pain. N. Eng. J. Med., 228:564, 1943.
5. Graner, E.: Pruritus Ani. Etiologic Factors and Treatment in 100 Cases. N. Eng. J. Med., 223:1015, 1940.
6. Drueck, C. J.: Essential Pruritus Perineci. J. Nerv. & Ment. Dis., 97:528, 1943.
7. Sack, E.: Derm. Wehnsch., 84:16, 1927.
8. Stokes, J. H.: Masochism and Other Sex Complexes in the Background of Neurogenous Dermatitis. Arch. Derm. & Syph., 22:803, 1930.
9. Rosenbaum, M.: Psychosomatic Factors in Pruritus. Psychosom. Med., VII:52, 1945.
10. Ferenczi, S.: Int. J. Psych. Anal., 6:380, 1925.
11. Saul, L. J.: Incidental Observations on Pruritus Ani. Psycho. Anal. Quart., 7:336, 1938.

Pyrosis

An Analysis of Its Clinical Significance and Pathogenesis

By

G. W. H. SCHEPERS

JOHANNESBURG, S. AFRICA

INTRODUCTION

IT IS PROBABLY TRUE to say that chronic dyspepsia is a disorder of much greater social significance than malignant disease of the alimentary tract. For the latter merely kills the patient, usually at a time when he is reaching his allotted span of three score years and ten. And if neoplasm does not achieve this merciless result, some other disease will probably do so. The only cause for regret to the relatives and friends is, in many instances, the attendant suffering or the expense incurred. Cerebral haemorrhage is so much quicker and cheaper.

But dyspepsia affects many persons in the prime of life; often the most active or influential members of society; often the breadwinner of the family. It not only subjects its victim to slow torture, but, what is more important, generates in him a mood of truculent irritation, unless it be this mood which is the cause of the dyspepsia. A dictator with dyspepsia is likely to be a much more dangerous epi-phenomenon of civilization than one with a carcinoma. The indigestion of the one may inflame him to acts of aggression or revolution, while the neoplasm of the other may weaken him into toleration or reform. Democracy differs from totalitarian society apparently in the greater variety and multiplication of the lesser despots. We all meet with the little tyrants daily, but it is only the doctor who is likely to recognise that the responsible personality trait may be partly at least linked with a symptomatic disorder.

Not the least significant of these is pyrosis. The op-

pressive, burning sensation below the xiphi-sternum, associated with acid eructations, pain at the inferior angle of the left scapula, flatulence, etc., is daily reported to the average practitioner. And yet it seems to have eluded either correct explanation or appropriate treatment. As proof of the latter we have the great diversity of proprietary and pharmaceutical remedies recommended. If its etiology or pathogenesis were completely understood the average textbook of medicine should volunteer more information than it does. Hunt (*British Encyclopedia of Medical Practice*, V. 9, 1938) confines his statement to the observation that it "is not always associated with a high gastric acidity, and though found in ulcer cases, is also common in gastritis and in gall-bladder disease, in some cases with achlorhydria." This statement from such a standard work of reference implies that pyrosis is most commonly related to hyperchlorhydria. At least, this is the most universally accepted view about its clinical significance, and ant-acid preparations are commonly administered to the patient on the presumption that the complaint indicates an excessive secretion of gastric acids. And yet, so far from finding literature to prove that pyrosis is most commonly found in association with hyperchlorhydria, I can discover no satisfactory evidence that it is necessarily related to hypersecretory activity of the stomach.

In fact, it is so commonly found in association with achlorhydria, that one may conclude that it is more likely to be due to this disorder, or at least has nothing to do with the presence or absence of hydrochloric acid in the stomach juices.

With the object of discovering the significance of this peculiar complaint I rejected all preconceived no-

*University of the Witwatersrand, Johannesburg, South Africa.
Submitted February 10, 1946.

tions about it and investigated a series of cases in which pyrosis had been a marked and chronic complaint and one of the presenting symptoms at first consultation. The results of the first hundred cases selected at random are given here. So many patients attend with this symptom that it should be possible ultimately to treat the clinical and laboratory findings statistically with the object of establishing exact correlations. In this preliminary account, observations expressed as percentages where possible must suffice to convey the clinical impression formed concerning this disorder.

ASSOCIATED CLINICAL FEATURES

Age and Sex Incidence

No age seems to be exempted. But pyrosis is distinctly more common and severe in the third and fourth decades. The sexes seem to be about equally affected in my series, males possibly more frequently. But in respect of this factor a great deal depends on the type of practice one conducts. During this investigation I had occasion to examine many more female patients than males. There is therefore probably a relatively higher incidence in male patients.

Body Habitus and General Features

As the type of case one deals with will be partly determined by the artificial limitations of occupational specialism, it is risky to express an opinion on this subject. In the series examined the greatest number of patients were of Sthenic to Pyknic habitus; 75% admitted recent or progressive excessive gain in weight, while 10% complained of loss of weight. The personality varied between Epileptoid and Hysteroid, but included several Cycloids and Schizoids.

Almost all of the patients complained of associated fatigue and lassitude, the majority also reported manifest asthenia. Sensations of swelling, mostly referred to the abdomen, wrists and ankles, and usually rather vaguely described and ill-defined, were reported by at least two-thirds of the patients. On examination, slight oedema of the ankles, not associated with any material impairment of cardiac function, was found in 15% of cases. On the other hand, myxomatous deposits were demonstrable over the nape of the neck, the supraclavicular fossae, the axillae, popliteal fossae, and round the wrists and ankles in 55% of the cases of this series. As many patients referred to sensations of burning of the conjunctivae, stiffness of the eyeballs with retro-ocular pain, worst in the mornings. But in only a few could any distinct eye-disease be displayed, apart from refraction errors which were relatively common. In a few cases moderate degrees of exophthalmos together with sympathetico-tonic pupillary reactions were demonstrable. In a larger proportion puffiness of the lower eyelids was fairly obvious. The skin tended to be dry with hypo-hidrosis in most cases, and with striae atrophicæ over the shoulders and hips in several instances. Hair growth seemed to be impaired in at least

70% of cases, the hair also tending to be dry and to fall out, with early baldness in men. Pruritus was recorded in 45% of cases without any discoverable external lesion. Pruritus ani and vulvae were commonly mentioned. Pallor was present in 60% of the cases. Another 15% had a florid complexion.

Alimentary Tract

The pyrosis displayed no peculiar features in this series. It varied in intensity and duration. The majority of patients (70%) referred its time of maximal intensity to the period between meals; in 20% it occurred shortly after meals, and only in 10% was it commonest immediately before meals.

Its commonest co-symptom was flatulence (85%). Flatus excess was reported by at least half the patients. A sensation of distension, especially after meals, or at night, was associated with this flatulence in 72% of cases. Constipation was present, and usually severe, in 75% of cases; diarrhoea occurred but seldom. Acid eructations were not invariably present, as the average definition of pyrosis implies; water-brash was present in only 12% of the cases. Nausea occurred in 20%, while vomiting was uncommon, many patients volunteering this information that they find it "impossible" to vomit when occasionally required to do so. This preoccupation with the need for reversed peristalsis of the upper alimentary tract suggests that nausea is probably commoner than stated. Anorexia (relative) was present in 62%. Excessive or untimely hunger was uncommon.

Definite food allergy was established in only 9% of cases; but food dislikes were fairly common; and food cravings sometimes as strange as they were irresistible. Episodic pain associated with meals occurred in about half the cases. It assumed the character of a hunger pain in most instances. In others pain was immediately evoked by eating. Its character and distribution did not warrant the diagnosis of peptic ulceration in more than a few instances. But both the pain and the pyrosis were slightly relieved by alkali's in 20% of these cases; by water in 40%; by dilute hydrochloric acid in 36%; and by reducing the carbohydrate content of the diet in 25% of cases. In my proved uncomplicated peptic ulcer cases pyrosis was rarely reported. Dysphagia was complained of in 24% of cases. Glossitis was observed in 15%; dental caries was present in 65%; pyorrhoea in 7%, and gingivitis in 24%.

On examination distension of the stomach was found in 65% of cases, the upper abdomen being markedly tympanitic in most of these cases. Focal tenderness over the topographical area corresponding to the anatomical limits of the stomach and duodenum were observed in 15% of cases only. But the liver showed slight enlargement in 80% of cases, though in other respects not suggestive of impaired function or active disease. Chronic cholecystitis and chronic appendicitis were but rarely diagnosable. Spasm, tenderness, distension and thickening of the descending colon were however de-

monstrable in at least 30% of cases. Haemorrhoids were complained of in 72%.

Gastric analyses revealed hypochlorhydria in 84% of cases; achlorhydria was less common. Free hydrochloric acid was increased in 6% of cases only; while other acids were present in increased concentration in 10% of cases. Neither the administration of acid nor of alkali aggravated the pyrosis.

Roentgen examination of the upper alimentary tract demonstrated duodenal ulcer in only 7% of cases and gastric ulcer in none. In 33% of cases there was an irritable duodenal cap with suggested duodenitis. Hypertrophic gastritis was suggested in 16% of cases. Cholecystography was negative in all but 4% of cases. But evidence of inflammatory or irritative lesions in the descending colon could be displayed radiographically in at least 25% of cases.

Respiratory System

Frequent colds were reported in 45% of cases. Sinusitis was relatively uncommon, and ingestion of a post-nasal discharge or of septic matter from diseased tonsils appeared not to be a factor in these cases. Pulmonary disease was not sufficiently common to merit consideration in the etiology of the condition. Shortness of breath on the slightest exertion was a complaint in the majority of patients, but at rest there was not marked dyspnoea.

Cardio-vascular System

Palpitations were complained of by almost all these patients. Fainting occurred in about half, vertigo being even more common. Bradycardia was present in 60%; Tachycardia in 12%. The blood pressure was slightly raised in 36% of cases. Hypopiesia, however, was more common, 54% showing systolic pressure readings of less than 100 mm. Hg. Yet cardiac impairment was uncommon, and where present clearly attributable to valvular disease or coronary sclerosis. Arteriosclerosis was clinically detectable in only 12% of cases, and even in these relatively slight, though remarkable for being present in such young subjects. Varicose veins were uncommon.

Haemopoietic System

Blood-examinations revealed moderate anaemia in 22% of cases. Of these two-thirds were of the microcytic normochromic to hypochromic variety; one-third tending to moderate macrocytosis and hyperchromia. The relatively high colour indices established were out of proportion to the mean corpuscular volume, so that a factor of relative hydraemia could be suspected in most of these anaemias.

The fasting blood sugar was reduced to hypoglycaemic levels in 11% of cases only. Diabetes mellitus was a factor in only two cases. The blood urea was raised slightly in two other cases. The blood cholesterol tended to be raised in a high proportion of these patients, exceeding 400 mgms. % in 33% of cases.

Urinary Tract

In this department many of the patients were museums of pathology. It is possible that Bilharzia may be incriminated in several cases; but the specific lesions and the excretion of ova could be displayed in only a few cases. More commonly the diagnosable pathology comprised non-specific infections of the lower and upper tracts, together with relative obstruction. Venereal disease was not a factor in more than a few of these cases, the patients either having been exposed to infection but seldom, or having been cured at an early stage and withholding this information. Infection of the upper urinary tract alone (if this be possible) occurred in 33% of cases; at any rate, the weight of clinical evidence was on these regions in these cases. "Pure" infection was present in 12% of cases only, being then of an intermittent variety, easily cured, but returning as readily. The pathogenic organisms in these cases were mostly *B. coli*; but streptococci and staphylococci were not uncommon. In the majority of these cases of infection of the upper urinary tract the inflammatory signs involved the upper two-thirds of the ureters, as well as the renal pelves. In some the brunt of infection fell on the vesical orifices of the ureters. In the cases of lower urinary tract infection the diagnosis of prostatitis and vesiculitis could be established digitally, urethroscopically and microscopically.

Relative obstruction in the urinary tract was present, however, in most of these cases of infection. In about one-third of cases it was probably merely inflammatory in character, especially in the cases of prostatitis and ureteritis. In a larger proportion of cases regional interstitial fibrosis had supervened, rendering necessary painful dilatations and resections.

Albuminuria and glycosuria were rare.

Genital System

Lack of libido was a common complaint; secondary hypo-sexualism was at the basis of this. To judge by menstrual abnormalities, hypogonadism was present in at least half of the cases, and relative sterility or impotence were features of other cases. Cervicitis was probably as common in the females as the prostatitis in the males. Both probably stood in the same relationship to the urinary tract infections and obstructions referred to. Occasional cases showed ovarian cysts or other rare gynaecological disorders.

Nervous System

Headache was almost invariably complained of. It was associated with confusion, somnolence and irritability in most instances. Depression and retardation were relatively uncommon, while the tendon reflexes appeared to be increased in 54% of cases and diminished in 24%. Tremor (fine to coarse) was complained of and observed in 31% of cases. Paraesthesias, referred mainly to the feet, the trunk, the hands and face, were reported in 95% of cases, and in most of these, areas of disturbed peripheral sensation could be mapped out.

Endocrine System

The thyroid was enlarged and hardened in 86% of these cases. The basal metabolic rate was decreased in two-thirds of these cases (ranging between —5 and —25) and increased in 10%. Even in the latter cases the clinical features suggested a mixture of hyper- and hypo-thyroidism and response to iodine therapy was unsatisfactory. Hypo-gonadism has already been referred to. Hypo-adrenalism was suggested clinically in 7% of cases and could be confirmed by means of water excretion and chloride retention tests in 26% of cases.

DISCUSSION

This exhausts the list of phenomena found in association with pyrosis in this series of cases. It seemed just as overwhelming to me at the time as it must appear to the reader now, unless he has already grasped certain of the obvious features which lend themselves to correlation within this collective case history. This summary of symptoms and signs is intentionally discursive to show by what devious route I arrived at the conclusions regarding pyrosis to be set out below, and to enable other investigators with better facilities and more patience and knowledge to subject my summary to detailed confirmation or refutation. I should however emphasize the fact that the cases I discuss herewith may possibly represent "freak" cases in as much as they formed part of a large collection of "chronics" of one of the largest Benefit Societies on the Witwatersrand, whose investigation and treatment had been entrusted to me. On the other hand, *Homo sapiens* is all of a part. It is likely that similarly well established cases can be found in any "civilised" community. The minor forms of pyrosis are fairly universally distributed and the germinal form probably affects the average person transiently at some or other time of his life. Yet these rather exaggerated cases are of value in providing one with virtual autopsy evidence of the underlying pathology. At an actual post mortem one is not likely to hunt for causes of pyrosis; it is known to be a "disease" which has probably never killed anyone. It is the living patient who is more likely to direct one's attention to his symptom.

On reviewing the series of symptoms and physical signs discovered in the present series of cases it must be obvious that some of these are negligible, whereas others are sufficiently frequent of occurrence to justify direct correlation. Taking, for instance, the features which occurred in association with pyrosis in at least 60% of cases, one finds that they comprise: gain in weight; distribution of pyrosis to the period between meals; flatulence and flatus; bloating; constipation; anorexia; distension of the stomach; enlargement of the liver; haemorrhoids; hypochlorhydria; fatigue and asthenia; effort dyspnoea; palpitations; vertigo; bradycardia; urinary tract infection and relative bilateral obstruction; hypo-sexualism; headache; somnolence and irritability; hyper-reflexia; paraesthesias; enlarge-

ment of the thyroid and diminished basal metabolic rate together with trophic changes in the skin. Pyrosis, occurring in association with such a high percentage of these symptoms and signs, must be related to their common cause or causes.

But the emphasis on the combination of these and other symptoms naturally differed from patient to patient; in each a tentative diagnosis of a pathological syndrome could be made; and these individual diagnoses again lend themselves to selective grouping. It was found possible to distinguish at least three fundamental pathologies, which again are interdependent and reciprocal in respect of pathogenesis or etiology. These are the diseases of the urinary tract; those of the endocrine system; and those of the alimentary tract proper. The first of these were commonest in this series; the latter least common. Urinary tract disorder could be demonstrated in 86% of cases; endocrine abnormalities were distributed over 64% of cases; while alimentary tract disorders could be diagnosed in 34% of cases. In 50% of the cases the endocrine dysfunction could be regarded as the major or even primary condition; urinary tract pathology was the basic feature in 38%; and in the remaining 12% alimentary tract disease could be incriminated.

In the case of the urinary tract disease the lesion was restricted to or maximal in the upper tract in about one-third of cases and distributed to the whole system but with emphasis of pathology on the lower tract in the remainder. Infection without diagnosable complication was a factor in 12% of urinary tract cases; infection plus obstruction was present in the remaining 24% of cases. And among the latter relative obstruction was *intermittent and due to inflammatory* turgescence of tissues in a third of the cases and due to structural or material, progressive changes in the other two-thirds of cases.

Among the endocrine disorders hypothyroidism was the major condition in 37% of cases; hypoadrenalism was the primary disease in 7% and hypogonadism in 6%. But evidence of the suppression of thyroid function could be demonstrated in all these cases of altered endocrine activity; relative hypoadrenalism was a factor in about a quarter and hypogonadism in about half, especially in the female patients.

The diseases of the alimentary tract had the lowest total incidence, despite the nature of the complaint. Chronic gastro-duodenitis was recognisable in half of these; colitis was a factor in a third of these alimentary tract cases. And colitis and gastro-duodenitis were again obviously associated with one another in two-thirds of the cases in which they were separately diagnosable. Cholecystitis and chronic appendicitis were rarities.

But the exponent of the single pathology school of thought will no doubt go even further than this and seek to link up the disorders of the above three affected systems. And if they all stand in relationship to a common symptom, namely, pyrosis, there may be justi-

fication for such endeavour. It must either be related to their common cause, if such there be, or they may separately cause the symptom and thus stand in relation to one another through subsidiary features of their individual pathology complexes. Yet the urologist will readily be able to protest that pyrosis is not found in all urological disorders. In fact, it may be present in so small a proportion of cases that it may have remained ignored by the specialist in this branch. The present analysis suggests that it is only found in cases of bilateral relative obstruction associated with chronic "benign" infection. The endocrinologist again may produce vast numbers of major endocrine disturbances in which it is absent. Likewise the gastro-enterologist will cite the majority of primary alimentary tract diseases as being pyrosis-free. Therefore, though I do not know whether it be a good or a bad thing to be stigmatised as an adherent of the single pathology School in diagnosis, I am constrained to find the explanation of the condition in terms of a single framework which would unite the above diversified conditions.

Moreover, this conviction was fortified by the evidence of successful therapeutics. The recommended palliative treatments for pyrosis reflect our ignorance on the subject by their uselessness. Treatment of the gastro-duodenal and intestinal disorders along ordinary dietetic and pharmaceutical lines was a little more successful in reassuring the patients that relief was imminent, but failed to cure the pyrosis, while the gastro-duodenitis and the colitis tended to recur on discontinuation of the therapeutic measures. Attention to the genito-urinary tract pathology brought about a great change in most patients. Apart from the local relief it afforded, many of the systemic symptoms abated. But particularly noticeable was the influence on the gastro-duodenitis and the colonic symptoms. Here then there is clearly some connection. Yet the pyrosis was one of the hardest complaints to yield. Much reduced in severity where treatment of the urinary tract disorder was adequate, it yet persisted until endocrine therapy was instituted, when it cleared up in most cases. The most effective general remedy was dried thyroid in appropriate dosage. Where the clinical condition warranted this, suprarenal cortical hormone and ovarian extracts, particularly corpus luteum preparations, were suitable adjuvants. Moreover, as the patients improved in general health, the dosage of these endocrine preparations could be discontinued. I do not think one ever cures these chronic cases completely, especially not where major urinary tract obstruction had been a long-standing factor. But it is possible to restore them to normal life and keep them comfortable by attention to the underlying conditions, lest recrudescence manifests itself from time to time. In the lesser forms of pyrosis it has been possible subsequently to bring about complete "cure" of the symptom by rectifying minor endocrine imbalances which may be present, and treating associated minor infections or irritations of the urinary tract and colon.

To integrate pyrosis with the three major disorders discovered, together with all their diversified associated phenomena, may even be possible on the basis of analogy. The clue to the necessary explanation may be found in the very nature of pyrosis itself. It is not a pain. Alimentary tract pain is caused by spasm or colic or by distension or by traction on the mesentery. Apart from these factors, or from irritation of the peritoneum (which is, embryologically speaking, not a constituent of the alimentary tract, though in subsequent ontogeny inseparably linked with its fate), no other form of ill-usage of the viscera appears to cause pain. What then can cause pyrosis? Ingestion of medicinal hydrochloric acid causes no immediate discomfort in the average subject; nor does neutralisation of the hydrochloric acid of the stomach by alkalis cause pain or discomfort. But most normal persons will experience transient deep-seated substernal discomfort which cannot be described as pain, on swallowing excessively hot or cold liquids. This may naturally be an oesophageal sign; or it may refer to transient spasm at the cardio-oesophageal junctional sphincter. The analogy which might, however, suggest an explanation is the case of peripheral manual or pedo-crural paraesthesia. Here too the patient reports spontaneous sensations referred to cutaneous territories innervated by peripheral nerves. But these sensations do not closely mimic the stimuli impinging on the nerve terminals in ordinary circumstances. In fact, paraesthesia is a unique phenomenon. *Perhaps pyrosis is a form of visceral paraesthesia*, referred to the gastric terminals of the splanchnic or the vagal nerves, and localised and exteriorised to the terrains of the 7th, 8th and 9th thoracic somatic nerves through the central association between the greater splanchnic nerve and the corresponding spinal segments. In my series of cases it is associated with peripheral paraesthesias, which responded to the same treatment as that which alleviated the pyrosis.

Peripheral paraesthesia may be a manifestation of irritation of the nerve at a distant point or of a remotely situated ganglion. Suitable pressure on the brachial plexus will refer paraesthesia to the fingertips. By analogy then, pyrosis, regarded as a type of visceral paraesthesia, may be a manifestation of irritation of ganglia at remoter situations within the complex network of the autonomic nervous system. Thus pyrosis may be a paraesthesia following reflex irritation of the coeliac plexus by a contiguous infected renal pelvis, or via the renal sympathetic plexus. It may again result reflexly via the inferior mesenteric plexus through irritation of Meisner's plexus in the lower colon. Or the source of the ganglionic irritation must be sought lower down in the hypogastric, vesical or pelvic plexuses, where local infection and irritation in the lower ureteric tract may be the responsible lesion. It is not difficult to find anatomical channels connecting these regions with the splanchnic or vagal nerves to justify the extension of the paraesthetic concept.

On the other hand, peripheral paraesthesia is com-

monly associated with hypothyroidism. The explanation for its etiology may lie in the mechanical changes in the nerve conduction through infiltrating myxomatous tissue; or must possibly be attributed to interference with tissue oxidation. Whatever be the pathogenesis, the association is undoubted. And the autonomic nerves differ more in respect to their distribution than with regard to their properties from the somatic nerves. If endocrine imbalance can produce acroparaesthesia, referred to the ulnar or the plantar nerves, say, there seems to be no material reason why pyrosis cannot also be thus caused, if it be a paraesthetic manifestation. It does seem to be the case that with the peripheral paraesthesia the localisation of the lesion may be determined by the presence of the confining anatomical straits traversed by the affected nerves and within which pressure effects may be generated in a swelling nerve or by a strictured canal, such as may result from fluid-logged tissues or nerves. The greater splanchnic nerves and the vagi are similarly confined where the former pierce the diaphragmatic crura and the latter are wedged between the oesophagus and the margins of the oesophageal opening of the diaphragm.

Though this neural theory of the syndrome may suffice to explain all its subsidiary features, I entertain yet a further hypothesis of a biochemical nature which may particularly assist in illuminating the association between gastric symptoms together with manifest gastro-duodenitis, on the one hand, and the infection plus obstruction within the urinary tract, on the other. The main function of the renal tubules appears to be re-absorption of water. Though their function is so specialised that they effect this without reabsorbing the various chemical excretions concentrated in the urine, yet

I cannot accept it that their cells were quite as cleverly designed as to reject all chemicals which may find their way into the urine. And where the pressure within the renal pelvis is increased it may well be that their inhibitory polarity may be reversed or altered. Breakdown products of bacterial metabolism may thus find their way into the blood stream. And these may then be excreted in the stomach or colon in the same way as foreign substances, such as morphine, for instance, continue to be re-excreted into the stomach after their absorption. Such an hypothesis may explain the origin of gastro-duodenal and colon irritations, and incidentally account for the origin of pyrosis even in those cases where it is present apart from any discoverable gastritis or duodenitis, but where infection plus relative obstruction may be demonstrated in the lower or upper urinary tract.

SUMMARY

- a) The significance of pyrosis is reviewed.
- b) Clinical features associated with one hundred marked cases of pyrosis are analysed.
- c) At least three pathological syndromes are related to pyrosis.
- d) These are referred, respectively, to the endocrine, urinary and alimentary tracts.
- e) These syndromes may be interrelated and on the basis of such an integrated pathology pyrosis may be capable of explanation.
- f) Argument is advanced to show that it may represent a variety of visceral paraesthesia.
- g) This paraesthesia may then be either reflexive, endocrinogenic, or due to gastro-duodenal irritation from toxic absorption.

Editorial

DR. R. WALTER MILLS, 1877-1924

DR. MILLS, a pioneer roentgenologist, published his great work on "*The relation of bodily habitus to visceral form, position, tonus and motility*," in the Am. Jour. Roentgenol., April 1917, IV, 155-169. He clearly demonstrated that mankind is divided into four great classes, viz: 1. Hypersthenic, 2. Sthenic, 3. Hyposthenic, 4. Asthenic. In 1922 an article appeared in the same journal on the "*Incidence of bodily habitus and the time of complete gastric motility in different types of habitus*."

In 1922 his paper on "*Small Intestinal States*" formulated the basic principles on which the roentgen diagnosis of lesions of the small intestine must rest.

This work is epoch making in character and establishes a clinical classification of anatomic and physio-

logic types so definitely that it is now employed by clinicians throughout the world, many of whom do not realize that Dr. Mills was the author of this tremendous original research work.

In his daily x-ray work he catalogued and filed his observations and thus collected clinical material which resulted in the solution of many important physiologic problems, such as the hypothesis of the transmission of gastro-intestinal tension, small intestinal recoil, peripheral colonic motility, etc.

Dr. Mills was really a martyr to his profession, dying of leukemia at the age of 47. At the time of his death he was president of the American Gastro-enterological Association. His name is destined to be inscribed among the Immortals in Medical History.

— H. W. Soper, M. D.

Book Reviews

Shock Treatments and Other Somatic Procedures in Psychiatry. By Lothar B. Kalinowski and Paul H. Hoch. Grune & Stratton, New York, 1946. 294 pages. \$4.50.

This book gives a comprehensive discussion of the new physical treatments in psychiatry. Somatic therapy of mental illness offers many points of interest to physicians working in other fields of medicine. The specialist in digestive diseases will be particularly interested in the discussion of Insulin Shock Treatment. The symptomatology of the various phases of hypoglycemia and the techniques to terminate the hypoglycemia are described in great detail. Modifications of the usual technique of insulin shock treatment and the treatment with divided doses, with rapidly increasing doses, with protamine zinc insulin, the intravenous injection of insulin are given. The technique of so-called ambulatory insulin treatment avoids comatous doses of insulin altogether while the "prolonged coma technique" tries to prolong the period of deep coma beyond the normal limit of one hour. Much interesting information for the specialist in metabolic diseases is offered regarding such questions like hypersensitivity to insulin, insulin resistance and allergic reactions. Cardiovascular and respiratory complications, epileptic attacks which occur more frequently before the stage of coma is reached, and some other neurological and psychiatric complications occur.

The most frequent complication is the prolonged coma in spite of ample application of sugar, and even though the blood sugar has returned to normal. It is obviously no longer a state of hypoglycemia but some alteration of the nervous system following the hypoglycemic coma. The chapter on medical observations and laboratory findings discusses the blood and spinal fluid sugar content and carbohydrate metabolism, changes in the vegetative nervous system and other findings. Pretreatment glucose tolerance curves reveal an abnormally prolonged interval before return to fasting levels. After treatment a direct correlation between clinical improvement and increased sugar tolerance, regardless of therapy was found. Insulin administration was not a determining factor. Some authors believe that the carbohydrate metabolism in schizophrenics with complete remission shifts toward the normal in the same way that the fat metabolism does.

A survey of results with insulin shock treatment in

schizophrenia shows that they depend entirely on an adequate application of the difficult technique. The same is shown regarding the newer Electrical Convulsive Therapy which replaced the previous pharmacological convulsive treatment with metrazol. Electric convulsive therapy, aside from schizophrenia, is applied in manic depressive psychoses, involutional psychosis and some other conditions. There are hardly any contraindications to this treatment, although a number of unpleasant and mostly unpredictable complications are discussed in much detail. One of the dangers is bleeding from active peptic ulcers and rupture of an ulcer or of an inflamed diverticulum during the convulsive treatment. Medical observations during electrical convulsive treatments have been made in great number but offer fewer points of interest than those made in insulin treatment. Many humeral studies are listed in the text, and investigations of gastric secretion and gastric contraction are mentioned. Of endocrine-neurovegetative effects, gain of weight is the most constant clinical change under convulsive therapy. This is considered by some as evidence of a diencephalic effect that not only insulin treatment but also electric and other convulsive therapy leads to such gain of weight.

Aside from various techniques to combine insulin and convulsive therapy, other somatic treatments in psychiatry are discussed such as various pharmacotherapeutic attempts, continuous sleep treatment with large amounts of barbiturates, fever therapy, nitrogen inhalation treatment, vascular shock (acetylcholine), histamine, methylguanidine and others. The newest physical approach to mental illness is brain surgery (prefrontal lobotomy), a procedure which in properly selected cases can be of great benefit after all other methods have failed.

The book, which starts with a chapter on the historical development of somatic treatment in psychiatry, closes with a chapter on theoretical considerations. Many theories have been offered for the explanation of the new treatments which are so successfully applied, but the authors close with the frank statement that "we are treating empirically disorders whose etiology is unknown, with treatments whose action is also shrouded in mystery." The book contains a bibliography of more than 600 items and a subject index.

—*Franz J. Lust, M. D.*

CORRECTION

In an article by Brown and Rivers on pages 33-36 of the February, 1945 issue, the authors desire to make a correction in the eleventh line of the third paragraph

which should have read as follows: "Histamine was then injected subcutaneously in doses of 0.1 mg. per 10 kilograms of body weight."

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Microfilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Microfilm Service, Army Medical Library, Washington, D. C.)

M. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
WM. D. BEAMER
IVAN BENNETT
J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

R. L. BURDICK
R. E. CAPPS
F. X. CHOCKLEY
C. G. CLEMENTS
JOHN I. COX
H. W. DAVENPORT
E. R. FEAVER
CARMELA FORDERARO
S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHIKIS
I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
FREDERICK H. SCHARLES

N. M. SMALL
G. M. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

* With the Armed Forces.

RUBEL, V. M.: *Lactic acid in gastric juice in various gastric diseases.* (Bull. Exper. Biol. Med., v. 18, p. 46, 1944).

In normal individuals, there was found from 1.5 to 2.5 milligrams of lactic acid per hundred cubic centimeters of gastric juice. The concentration remains unchanged in peptic ulcer but is slightly increased in pellagra and very markedly increased in certain gastritis.

SCHULTE, K. E.: *The liver fat of rabbits poisoned with phosphorus.* (Biochem. Zeitsch., v. 313, p. 78, 1942).

The higher fat content of the livers of rabbits poisoned with phosphorus can be prevented by feeding either large amounts of the vitamin B complex or unsaturated fatty acids.

UVNAS, B.: *The gastric secretory excitant from the pyloric mucosa.* (Acta Physiol. Scand., v. 6, p. 117, 1943).

The substance extractable from the pyloric mucosa ("gastrin") is destroyed by pepsin, trypsin and boiling in alkaline medium. It is thermostable in acid. The substance is soluble in water and dilute acid and alkali but insoluble in ether, acetone, absolute alcohol and benzene.

Low, H.: *The etiology and clinics of infectious hepatitis in the Terezin concentration camp.* (Casopis Lekaru Ceskych, vol. 85, No. 28, pp. 976 - 980, 1946.)

The patients were most contagious in the pre-icteric stage. The disease began with fever, conjunctivitis, pharyngitis, nausea and pain in the gastric region. In many cases, after one to three days, a short remission was observed. Later evening temperatures developed, with pain in the liver region. The stools were lighter but not acholic. The blood showed often eosinophilia. After 6 to 10 days, icterus set in. Proteinuria and hematuria were frequent. The liver, chiefly the left lobe, was enlarged. Pruritus and spleen tumor were rare. The convalescence was very long. Death occurred only in a few cases, under the picture of a

hemorrhagic diathesis. Author believes that the different clinical symptomatology is due to the bad general state of the inmates of the concentration camp.

O. Felsenfeld.

BRESKY, J.: *The Gros reaction.* (Prakticky Lekar, vol. 26, No. 9, pp. 259 - 261, 1946.)

The Gros reaction is performed by adding Hayem's solution, drop by drop, to 1 c.c. serum. In normal sera, the addition of about 2.66 c.c. of the reagent causes cloudiness and 3 c.c. an irreversible precipitation, while pathologic sera show such changes after the addition of less Hayem's solution. Hayem's solution consists of 0.5 Gm. sublimate, 5 Gm. sodium sulphate and 2 Gm. sodium chloride in 200 c.c. distilled water. Author compared this reaction with Takata's and found it helpful in the diagnosis of liver damage.

O. Felsenfeld.

BRAZDA, L.: *The importance of anesthesia in gastric operations in old people.* (Lekarske Listy, vol. 1, No. 12, pp. 283 - 286, 1946.)

In order to avoid shock (a complication author fears in old people during gastric surgery), local anesthesia combined with drug narcosis, e.g., scopolamine-morphia, or scopolamine-morphia-eucodal-ephedrine, was used. Of 41 patients over 60 years of age only two died, one following embolism, the other of heart insufficiency, when this type of anesthesia was applied during stomach and duodenal operations.

O. Felsenfeld.

WIRTH, T. K.: *Bilirubin and the pathogenesis of jaundice.* (Acta Med. Scand., v. 123, p. 166, 1946.)

In 35 cholecystectomized patients with common duct drainage the output of bilirubin per 24 hours was found to be between 50 and 250 milligrams. The level of the blood bilirubin in biliary obstruction was dependent on a balance between bilirubin production and its renal excretion. Therefore in complete obstruction the degree of jaundice is determined by the rate of bilirubin production.

Increased Excretion of Glucuronates After Ingestion of Benzoic Acid By Patients with Damaged Liver*

By

I. SNAPPER, M.D.,
A. SALTZMAN, M.D.,

and

E. GREENSPAN, M.D.

NEW YORK, N. Y.

IN a previous publication (1) it has been shown that after ingestion of sodium benzoate by normal volunteers excretion of considerable quantities of urinary glucuronates occurs only when the benzoate absorption takes place at a rapid rate. Under these circumstances, the quantity of benzoate suddenly absorbed from the gastrointestinal tract is so great that the liver is unable to conjugate all the benzoate with glycine to form hippuric acid. The excess of benzoate which cannot be quickly combined with glycine is linked with glucuronic acid and excreted as benzoyl glucuronate. When the absorption of the benzoate from the intestine takes place at a slow rate no benzoyl glucuronate is formed. Ingestion of 5.8 grams of sodium benzoate divided into nine equal parts and ingested slowly over a 4-hour period, yields no demonstrable glucuronate excretion. Furthermore, in contrast to sodium benzoate, the ingestion of a single dose of five grams of the less readily absorbable benzoic acid by normal volunteers results in no urinary glucuronate excretion. This is of both theoretical and practical significance.

The following report makes it clear that after ingestion of benzoic acid the amount and pattern of glucuronate excretion in patients with impaired liver function differs significantly from the glucuronate excretion of normals.

METHODS

The methods used are the same as reported in a previous publication.†

RESULTS

1. After rapid ingestion of 5.8 grams of sodium benzoate, patients with a damaged liver (Table 1) excrete considerable amounts of hippuric acid in the third 2-hour specimen. In this specimen the glucuronate reaction is without exception positive. In normal persons the third 2-hour urine specimen usually contains only small quantities of hippuric acid and the glucuronate reactions are without exception negative.

*From the Second Medical Service of the Mount Sinai Hospital, New York City.

†It should be stressed that the Tollen's naphthoresorcinol reaction was specially adapted for our purposes. These experimental conditions should be strictly applied to get comparable results. In the reading of the color,—which is done immediately following the extraction with amyl alcohol,—only a true blue color is considered to represent a positive reaction.

Submitted April 11, 1946.

2. After ingestion of 5 grams of benzoic acid by patients with liver damage (Table 2) the hippuric acid excretion is in the third 2-hour specimen always larger than has been found in normal volunteers. *In contrast to the findings in normal volunteers after ingestion of 5 grams of benzoic acid the glucuronate reactions in the urine of patients with a damaged liver are always strongly positive.*

In these patients the first 2-hour specimen shows often, and the second 2-hour specimen without exception, a strongly positive glucuronate reaction. The third 2-hour specimen is also frequently positive.

3. The same contrast between normal volunteers and patients with liver damage is found when 5.8 grams of sodium benzoate are slowly ingested in the course of 4 hours. (Table 3) Whereas under these circumstances the urine of normal volunteers shows no increase of the glucuronate content, in patients with a damaged liver function the first 2-hour specimen shows often, the second 2-hour specimen always positive glucuronate reactions; in the third 2-hour specimen these reactions are nearly always, and in the fourth 2-hour specimen often positive.

Table 4 shows the averages of the glucuronate and hippuric acid excretions in these experiments.

The abnormal pattern and amount of glucuronate excretion are constant signs of liver damage.

DISCUSSION

These studies show that after slow ingestion of sodium benzoate or of benzoic acid, the impaired formation of hippuric acid in the damaged liver leads to an increase of the glucuronate excretion. This result is so constant that the study of glucuronate excretion after ingestion of benzoic acid may be used to decide about presence or absence of liver damage. *If after ingestion of 5 grams of benzoic acid (or after the slow ingestion of 5.8 grams of sodium benzoate in the course of 4 hours), none of the three 2-hour specimens shows a positive glucuronate reaction, then the liver function can be considered to be normal.* It will be brought out that this increased glucuronate excretion after administration of 5 grams of benzoic acid is closely connected with the impairment of the hippuric acid synthesis in the damaged liver. The increase of the glu-

curonate excretion is, however, a more sensitive test than the diminished hippuric acid excretion as devised by Quick.

In Table 1, 2, and 3, several examples can be found of patients recovering from hepatitis where the hippuric acid excretion after ingestion of benzoic acid or sodium benzoate had already returned to normal but where the abnormal pattern of the glucuronate excretion still indicated liver damage.

Furthermore, certain technical and practical advantages are offered by the semi-quantitative measurement of glucuronate excretion compared to the quantitative determination of hippuric acid. The determination is simple. Urine samples rather than complete volumes of urine are necessary. Results are promptly obtained; for there is no necessity for a two-day delay for the tedious evaporation of large amounts of urine, and the weighing or titration of precipitates.

At first view an increase of the excretion of glucuronates after ingestion of benzoic acid in the presence of a damaged liver seems to be at variance with the formerly accepted concept that in the damaged liver the glucuronate conjugation is impaired. However, most of the evidence for the former theory has been based on the ingestion of such substances as menthol, phenol, and borneol, which are not conjugated with glycine. The studies of Boku and Kin on humans revealed decreased excretion of camphor glucuronate after ingestion of 0.5 grams of camphor in patients with cirrhosis. (2) This was also found in the later stages of liver carcinoma although in the early phases of this disease the glucuronate conjugation did not seem to be impaired. In hepatitis impairment of the conjugation of camphor with glucuronic acid ran parallel with the degree of jaundice. In experimental liver damage in rabbits caused by phosphorus and carbon tetrachloride, the diminution of the glucuronate production was stated to be proportional to the liver damage. These results are in contradistinction to recent studies by Kensler, Young and Rhoads (3) who demonstrated no impairment of conjugation of *d*, 1 borneol with glucuronic acid in slices of livers of rats with cirrhosis and hepatoma produced by butter yellow. Furthermore, after 40 days of feedings with dimethylaminobenzene (butter yellow) there was no impairment of urinary glucuronate excretion. Only after butter yellow has been fed for 100 days the glucuronate excretion diminished to less than 25% of the normal values. Beuding and Ladewig (4) reported impaired conjugation of borneol by slices of livers of guinea pigs after phosphorus poisoning but no impairment after chloroform poisoning. Also Ottenberg's (5) investigation of the excretion of glucuronates after administration of 1 gm. borneol to patients with impaired liver function gave only equivocal results. Four of his patients presented an increased glucuronate excretion whereas the remainder showed inconstant

amounts of glucuronate excretion. These studies demonstrate that in the presence of severe liver insufficiency in animals and man, administration of borneol is, at least occasionally, followed by excretion of increased amounts of glucuronate.

In contrast to the varying results after ingestion of camphor and allied products, the glucuronate excretion after ingestion of benzoic acid is constantly and significantly increased in patients with a damaged liver. As a matter of fact, Quick in 1931 (6) already observed in one patient with an alcoholic liver an increased glucuronate excretion after ingestion of sodium benzoate. After the liver condition had improved the glucuronate excretion after the ingestion of sodium benzoate had practically gone down to zero.

To understand the increased excretion of benzoyl glucuronate by patients with liver disease, it should be emphasized that the damaged liver has lost a considerable part of its power to form hippuric acid. Since the synthesis of hippuric acid is lagging in the damaged liver, here even slow absorption of sodium benzoate or of benzoic acid will lead to the presence of free benzoate in the liver. The benzoic acid which is not transformed by the liver to hippuric acid will be, as is always the case, conjugated with glucuronic acid. Therefore, in the presence of impaired liver function an appreciable glucuronate production will occur even after slow ingestion of sodium benzoate or after the administration of benzoic acid.

This result seems paradoxical because an increase of the benzoyl glucuronate excretion takes place although the glucuronate conjugation is impaired in the damaged liver. The explanation may be as follows. Due to the decreased rate of hippuric acid synthesis, so much more free benzoic acid is made available in the damaged liver for glucuronate conjugation that even in the presence of an impaired glucuronate mechanism the quantity of benzoyl glucuronate finally synthesized is larger than in normal volunteers.

Our results show not only the increase of glucuronate excretion, but also the impairment of the rate of glucuronate conjugation in the damaged liver. The latter appears from the following observation. Whereas in normal persons after ingestion of 5.8 grams of sodium benzoate the first 2-hour specimen always shows a strongly positive glucuronic acid reaction, in patients with liver cirrhosis this reaction is frequently negative in the first 2-hour specimen, to become strongly positive in the second and third 2-hour specimens.

It is now also possible to formulate an explanation of the varying quantities of borneol glucuronate excreted in liver patients after ingestion of borneol by mouth. It has to be considered that in normal persons after ingestion of borneol only about 50 per cent of the borneol appears in the urine as borneol glucuronate. The rest of the borneol disappears and is evidently metabolized. In the damaged liver the oxidation of

the borneol is certainly impaired: often, therefore, not 50 per cent of the borneol ingested but practically all the borneol ingested becomes available for the formation of borneol glucuronate. This increased quantity of borneol, available for conjugation, may lead, even in the presence of an impairment of the glucuronate conjugation, to an increase of the total amount of borneol glucuronate excreted by liver patients compared with the figures obtained in normal controls.

SUMMARY

After ingestion of 5 grams of benzoic acid by patients with liver cirrhosis or hepatitis the glucuronate reactions are always positive in the second 2 hours' urine specimen, usually also in the first and third 2 hours' specimen.

This glucuronate excretion is a sensitive liver function test. If after ingestion of 5 grams of benzoic acid, none of the three two-hours' specimens shows a positive glucuronate reaction, serious liver damage as accompanies hepatitis or cirrhosis is not present.

The increased glucuronate excretion after ingestion of benzoic acid by patients with a damaged liver depends on the impairment of the hippuric acid synthesis in the damaged liver. This leads to the presence of large quantities of free benzoate in the damaged liver which is conjugated with glucuronic acid.

At the same time in the damaged liver the synthesis of benzoyl glucuronate is slower in rate than under normal conditions.

TABLE II

5.0 grams of Benzoic Acid by mouth (rapid ingestion)

	NAPHTHORESORCINOL REACTION			HIPURIC ACID		
	I	II	III	I	II	III
Normals	-	±	-	2.69	3.21	0.853
Sh.	+	++	+++	1.115	1.42	1.29
Marb.	-	++	±	0.27	0.35	1.03
Berg.	-	+++	±	0.28	2.43	1.70
Con.	-	+	+++	1.00	1.41	1.87
Hend.	±	+++	+++	1.05	1.20	1.02
Rog.	+++	+++	+++	1.14	1.72	1.64
Vill.	±	+++	±	1.02	2.93	1.83
Zan.	±	+++	-	1.91	2.26	0.70
Riv.	-	+++	±	1.93	3.01	1.47
Mos.	+++	+++	±	0.83	1.04	0.70
Beck	±	+++	+++	0.65	1.00	2.03
Rot.*	+++	+++	±	1.96	2.57	1.67
Alv.	-	++	+++	0.98	2.20	2.03
Doug.	+++	+++	+++	1.92	1.93	1.17
Sha.	+++	+++	+++	1.30	Lost	1.28
Cad.	-	+++	+++	0.60	1.64	2.76
Seg.	-	+++	±	0.59	3.70	1.24
Led.	±	±	-	0.56	2.17	0.71

* Patient almost recovered from hepatitis.

Cirrhosis of Liver

Hepatitis

TABLE III

5.8 grams Sodium Benzoate by slow ingestion

	NAPHTHORESORCINOL REACTION				HIPURIC ACID IN GRAMS			
	I	II	III	IV	I	II	III	IV
Normals	-	-	±	-	2.17	2.92	1.65	0.35
Sh.	+++	+++	+++	±	0.93	1.27	1.35	0.44
Berg.	++	++	±	±	1.13	2.00	0.51	0.06
Mar.	-	+++	+++	±	-	1.23	0.30	0.45
Hend.	-	+++	+++	+++	0.44	1.22	1.34	1.04
Con.	-	++	+++	±	0.93	0.84	1.47	1.61
Vill.	-	+++	±	-	0.82	1.59	1.16	0.26
Rog.	-	+++	+++	-	1.58	2.20	1.98	0.58
Beck.	-	+++	+++	-	0.43	1.47	1.59	0.94
Mos.	-	+++	+++	-	0.17	2.10	1.71	1.04
Riv.	-	±	±	-	1.89	2.71	1.47	0.27
Hick	-	+++	+++	±	0.71	1.78	2.25	0.88
Meyr.*	+++	++	-	-	3.06	3.02	0.54	0.23
Alv.	-	++	+++	-	1.24	0.96	2.12	0.66
Doug.*	+++	+	±	-	2.68	1.17	1.75	0.62
Sha.	+++	+++	+++	+++	0.70	0.40	3.16	1.80
Cad.	+	+++	+++	+++	0.16	1.80	2.08	1.05
Seg.*	+	+++	+	-	2.44	2.01	1.44	0.60
Grat.	+++	+++	Lost	+++	1.68	3.91	Lost	0.07
Roth.*	+++	±	±	-	1.56	1.93	2.27	0.64
Led.	±	±	±	-	1.03	0.37	0.41	Traces
Moor	-	±	±	+++	0.17	0.29	0.08	0.41

* Patient almost recovered from hepatitis.

Cirrhosis of Liver

Hepatitis

TABLE I

5.8 grams of Sodium Benzoate by Mouth (rapid ingestion)

	NAPHTHORESORCINOL REACTION			HIPURIC ACID		
	I	II	III	I	II	III
Normals	+++	±	-	3.76	2.74	0.28
Sh.	±	+++	+++	1.21	1.11	0.64
Con.	±	++	±	1.04	1.58	1.64
Hend.	+	+++	+++	0.66	1.15	1.08
Rog.	+++	+++	+++	1.81	2.12	1.82
Vill.	+++	+++	+++	0.48	2.93	1.16
Mos.	±	+++	+++	1.26	1.85	1.62
Hick	+++	+++	+++	-	-	-
Meyr.	±	+++	+++	0.78	0.72	1.43
Alv.	+++	+++	+	Lost	1.31	2.25
Doug.	±	+++	+	0.27	3.02	0.74
Shaw.	+++	+++	+++	0.86	0.84	3.57
Cad.	+	+++	+++	0.43	3.0	2.23
Seg.	+++	++	+++	2.36	0.99	1.39
Rot.*	+++	+++	+	3.09	2.62	0.56
Moor.	+++	+++	+++	0.142	0.209	0.175

* Patient almost recovered from his hepatitis.

TABLE IV

NAPHTHORESORCINOL REACTION

HIPURIC ACID IN GRAMS

	I	II	III	IV	I	II	III	IV
Normals	+++	±	-	x	3.76	2.74	0.28	x
Liver cirrhosis	± to +++	± to ±	± to ±	x	1.04	1.78	1.27	x
Hepatitis	± to +++	± to ±	± to +++	x	1.30	1.80	1.74	x
Normals	-	±	-	x	2.69	3.21	0.85	x
Liver cirrhosis	- to +++	± to +++	- to +++	x	0.98	1.71	1.38	x
Hepatitis	- to +++	± to ±	± to +++	x	1.22	2.41	1.69	x
Normals	-	-	±	-	2.17	2.92	1.65	0.352
Liver cirrhosis	- to +++	+++	- to +++	- to +++	0.80	1.56	1.28	0.61
Hepatitis	- to +++	± to ±	- to +++	- to +++	1.71	1.89	1.85	0.72

I. First two hours urine specimen.

II. Second two hours urine specimen.

III. Third two hours urine specimen.

IV. Fourth two hours urine specimen.

5.8 grams of sodium benzoate (rapid ingestion)
5.0 grams of benzoic acid (rapid ingestion)
5.8 grams of sodium benzoate (slow ingestion)

TABLE V
COMPARISON OF STANDARD LIVER FUNCTION TESTS IN PATIENTS WITH
INCREASED EXCRETION OF GLUCURONATE AFTER INGESTION OF 5 GRAMS OF BENZOIC ACID

Bile	Urine	Urobil.	Icteric	Ceph. Flocc.	BSP	Cholesterol	Bilirub.	Alk. Phosph.	Prothr.	Time	Galactose	Excr. in Grams	Cirrhotic of Liver
			Index		Retention	and Esters	mgm %	Units %					
Sh.	F. Tr.	1:40	27			90	1.5	29	60%		7.1		
Berg.	F. Tr.	1:80	5	neg.	40%	180/90		35	79%				
Mar.	0	1:40	7		40%	330/245	0.2		80%		1.4		
Mos.	0	1:40			25%	380/190		54	80%		1.5		
Hend.	0	1:40	9			150/75	0.7	28	64%		6.6		
Con.	0	1:80	6		15-50%	100	0.3	8	70%				
Vill.	0	1:10	3			214	0.6	6			4.4		
Rog.	0	1:10				210/145		16	75%		4.1		
Beck.		1:40	12		60%				63%		3		
Riv.	0	1:10	8		10%		0.5						
Hick.		1:10	36			158	6.3	16	80%		3		
Meyr.	~	1:40	21	neg.		260/100	1.2	32			2.1		
Alv.		1:64	30		20%		2.1	35			7.6		
Doug.		1:20	33	neg.		760	3.5	46	71%				
Sha.		1:10	56			202	5.7	19			4.0		
Cad.		1:20	33			260/160	4.8	21	78%		4.3		
Seg.		1:2	18	neg.		273	0.8	54			3		
Grat.		1:256	12	neg.		219		6	82%		3		
Roth.		1:5	36			114		18					
Led.		1:10	33		10%	171	4.3						
Moore		1:20	36			120/	5.3		66%				

REFERENCES

1. Snapper, I., Greenspan, E., and Saltzman, A., Am. J. Digest. Dis. 13:275, Sept., 1946.
2. Boku, S., and Kin, I., J. of the Chosen Med. Association 21: 6*-7*, 1931.
3. Kensler, C. J., Young, N. F., and Rhoads, C. P., Proc. Soc. exper. Biol. & Med. 48:22-24, 1941.
4. Bueding, E., and Ladewig, P., Proc. Soc. exper. Biol. & Med. 42: 464-465, 1939.
5. Ottenberg, T., Wagreich, H., Bernstein, A., and Harrow, B., Arch. of Biochemistry 2:63-66, 1943.
6. Quick, A., J. Biol. Chem. 92:65-85, 1931.

Hypertrophic Gastritis Simulating Neoplasm*

By

Lt. Col. JOSEPH BANK,
MAJOR ALEXANDER E. PEARCE,
and

Lt. Col. JOHN H. GILMORE
M. C., A. U. S.

A 26 YEAR OLD white private was seen in the medical clinic of the William Beaumont General Hospital 28 March 1945 for symptoms suggestive of peptic ulcer. Roentgen ray examination on 30 March 1945 revealed an irregular round filling defect at the greater curvature side of the stomach suggestive of neoplasm (Fig. I). The stomach was empty in four hours. Before the patient could return to the clinic, he was transferred with his organization to another camp. A follow-up was instituted and as a result the patient was admitted to his station hospital, where roentgen study revealed findings similar to the above and a diagnosis was made of gastric tumor involving the greater curvature side anteriorly, moderately large, but without characteristics of malignancy. He was transferred to the regional hospital where an opinion of leiomyosarcoma, lymphosarcoma, or carcinoma was made by the roentgenologist. The gastroscopist there noted normal appearance of

the mucosa, but suspected an intramural tumor of undetermined origin. The patient was then returned to William Beaumont General Hospital for surgery.

The patient's symptoms began in 1937 and consisted of epigastric distress appearing two hours after meals and relieved by milk and food. A diagnosis of ulcer was made and relief followed institution of ulcer regimen. He felt fairly well for the following four or five years except for brief periods of distress following dietary indiscretion. During the past two years, exacerbations became more frequent. Since January 1945, the epigastric distress became more constant. Food failed to relieve the discomfort which seemed to persist until the stomach was empty. Following induction, his symptoms became worse because patient was unable to select his food. A weight loss of eight pounds was noted on admission.

Physical examination was negative with the exception of tenderness in the epigastrium. Laboratory studies including Kahn, blood count, urine, stool, icterus index, cephalin flocculation and serum protein were all within

*From the Medical Service, William Beaumont General Hospital El Paso, Texas.
Submitted December 14, 1945.

normal limits. Hyperacidity was present; fasting free HCl 90 total 110, highest postcibal acidity free 115 total 130. Roentgen examination confirmed previous impression of neoplasm and failed to demonstrate peristalsis in the involved area (Fig. II). Gastroscope showed a normal antrum and pylorus. At about the middle of the stomach the lumen was encroached upon by extremely large rugae on the greater curvature and extending more on the anterior than the posterior wall. There was no suggestion of polyposis, malignancy or intramural tumor. The surface of the mucosa was darker than normal, but otherwise smooth without suggestion of gastritis or erosion. It was believed that an exploratory laparotomy was indicated.

Operation was performed 5 July 1945. Palpation of

large and prominent, with extensive convolution. One ruga had a maximum width of 1.4 cms., while the maximum height was about 0.8 cms. Approximately 40 per cent of the mucosal surface appeared relatively smooth, with only one or two small rugae. The epithelial covering appeared everywhere intact. No trace of ulceration was observed anywhere. Portions of the epithelium showed numerous fresh reddish flecks, suggesting recent extravasation of blood. One of the rugae showed slight granularity between the mucosal fold. The adventitial surface was not remarkable. On section, the large folds showed a very thick mucosa, measuring up to 3.5 mms., with an exaggerated muscularis mucosa. The submucosa appeared greatly edematous, but no neoplastic masses could be observed grossly. The mus-

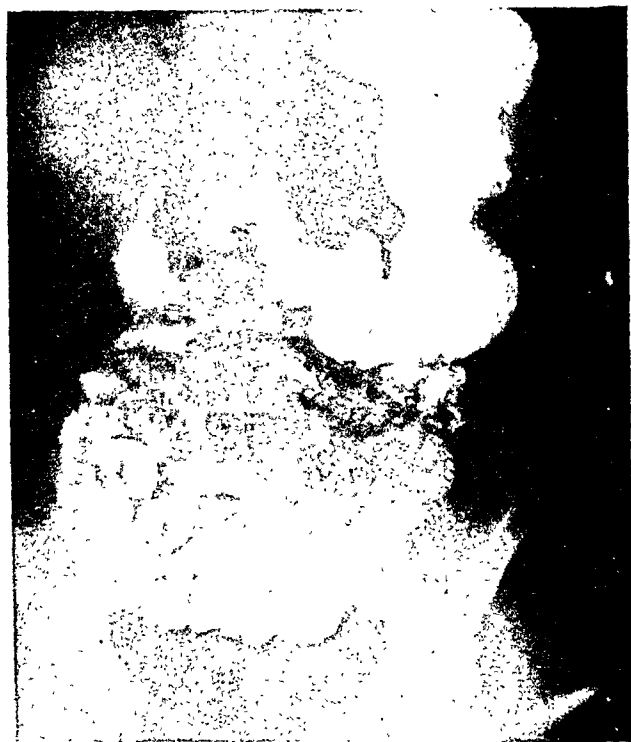


Fig. I — Roentgenogram of stomach, 1 April 1945.

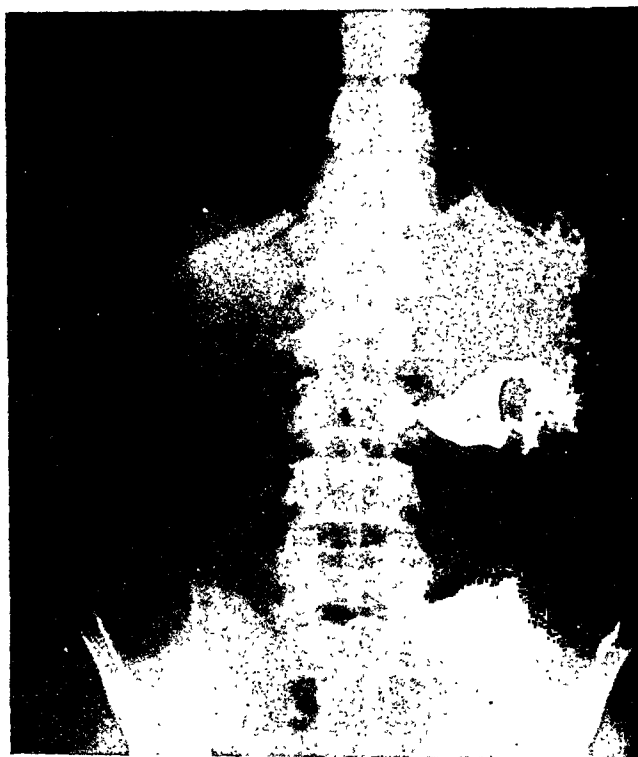


Fig II — Roentgenogram of stomach, 20 June 1945.

the stomach by the surgeon through the abdominal incision gave the impression of a polypoid tumor in the lumen of the stomach. A scar of an old pre-pyloric ulcer was observed on the anterior wall near the lesser curvature. A partial gastrectomy was gone. Upon opening the resected portion of the stomach, numerous hypertrophied rugae were seen in the area where the polypoid mass was felt. The surface of the mucosa appeared normal except for fresh superficial erosions of recent origin. A pancreatic rest was removed from the wall of the jejunum.

Pathologic study by Major Lester King showed the following:

GROSS (Fig. III): The specimen was a resected portion of stomach opened along the lesser curvature, measuring 12 x 12 cms., with a thickness of 0.7 cms. Over half of the mucosal surface, the rugae were very

cularis was distinct, measuring up to 2 mms.

MICROSCOPIC (Fig. IV): Numerous sections showing various portions of the stomach were available. Where the rugae were very large and prominent the mucosa appeared very broad, but with excellently preserved epithelium. In general, the glandular pattern was regular. In a few areas there was some dilatation, tortuosity, and irregularity of the glands, and disturbance of the normal even pattern. Some of these glands showed evidence of epithelial proliferation, manifested by piling up of epithelial cells, and papillary enfoldings into the lumen. Such areas, however, appeared entirely benign in character. The nuclei were regular and the basement membrane was respected everywhere. Within the stroma, which appeared occasionally slightly edematous, there was a definite excess of lymphocytes and plasma cells. In many zones numerous polys were visi-

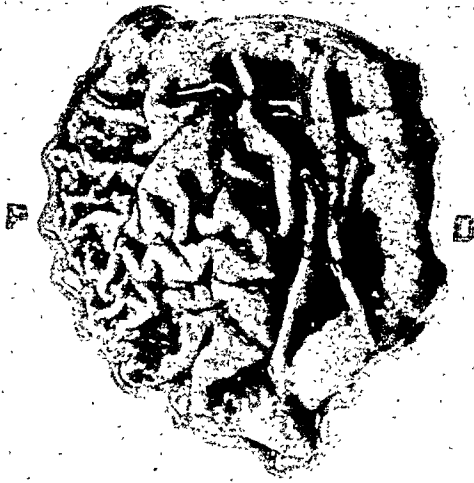


Fig. III — Resected portion of stomach opened along lesser curvature showing mucosal surface. P — proximal edge. D — distal edge.



Fig. IV — Cross section of stomach, low magnification.

inconsequential edema in some portions. The muscularis was of average or slightly increased thickness. Within the mucosa there were numerous lymphoid follicles.

DIAGNOSIS: Hypertrophic gastritis.

Recovery was uneventful and the patient was ambulatory in five days.

ble within the tunica propria, and some polys were seen within gland lumens. The submucosa showed a mild

Regional Enteritis and Idiopathic Ulcerative Colitis A Clinical Study*

B. J. WEINBERG, M.D.,
H. SORTER, M.D.

and

H. NECHELES, M.D., Ph.D.
CHICAGO, ILLINOIS

IN considering the etiology of regional enteritis and idiopathic ulcerative colitis we want to present a short review of the fields of investigation along with our data obtained on a review of 89 cases of these diseases.

Regional enteritis was first separated as a disease entity in 1932 by Crohn, Ginzburg and Oppenheimer. Their description of the physical findings was (1) a mass in the right iliac region, (2) evidence of fistula formation, (3) emaciation and anemia, (4) a previous appendectomy scar (50%), and (5) signs of intestinal obstruction. This description has certainly withstood the trials of time. Only one point, their description that by roentgen study there was only involvement of the terminal ileum, has been modified. It is now known that any portion of the ileum, not rarely the jejunum, and the colon to the rectosigmoid, may be

involved.

When we observe the incidence of regional enteritis, also called Crohn's disease, we find that it is increasing. And, while study has revealed that many cases formerly diagnosed as tuberculosis or malignancy were in reality regional enteritis, the increase is too steady and great. Thus, it is considered both a relative and an absolute increase.

While the Jewish race has been considered as having the greatest incidence, present work seems to indicate that this is not true. Likewise, the concept of a lack of familial occurrence is gradually changing. Crohn has seen the occurrence in more than one number of a family on four occasions. Brown and Schiefley report the occurrence in two sisters and one brother.

Interestingly enough we find that this disease does not occur in Latin America, and there has never been a case reported from the island of Cuba. Another interesting observation made by Bockus, is the absence of cases in families that have been in the upper economic

*Aided by a grant from the A. B. Kuppenheimer Fund. The Department is in part supported by the Michael Reese Foundation.

From the Department of Gastro-Intestinal Research, Research Institute and the Department of Medicine of Michael Reese Hospital, Chicago.

Submitted May, 1946.

bracket for a period of one or two generations. This makes one wonder, states Rockus, of the possibility of some factor of subnutrition with a heavy childhood infection.

When we look at age, most observers find 75% of their cases in the age group of twenty to forty. The disease is found at any age, but seldom in old people. Sex seems to play no part, although Crohn et al. reported a predominance of males in the ratio 3:2; but Bockus in twenty-one cases found eight males and 13 females; and Clark et al. in sixty-nine cases found no sex difference.

On looking through the work on etiology one is impressed by the significance attached to lymphatic involvement. The work of Hadfield and others has shown the importance of this observation, with the picture of lymphoid hyperplasia with giant-cells in the submucosa and lymph nodes, and by the presence of an obstructive lymphedema. The disease process seems to prefer certain areas of accumulations of lymphatic tissue. Most pathologists agree that, from an isolated viewpoint, the lesions of regional enteritis and tuberculosis cannot be differentiated. However, when the progress of the disease is studied as was done by Hadfield, one notices that upon regression, in regional enteritis there is a lack of scarring and caseation; also, the absence of tubercle bacilli has been noted. This makes one point clear, however, and that is the importance of differentiating a suspected case of regional enteritis from tuberculosis.

In 1933 Homans and Hass were struck by the resemblance of the histologic pictures of regional enteritis to that of Boeck's sarcoidosis. However, no work to date has proven any relationship.

Reichert and Mathes injected irritating and sclerosing materials into the mesenteric and submucosal lymphatics and produced chronic lymphedema of the intestine. When, in addition, they injected bacteria intravenously, they were able to produce even greater thickening of the bowel wall. Poppe repeated their work and obtained lymphedema of the bowel wall and ulcerations of the mucosa. However, this work has been repeated in this laboratory by Sinaiko and Necheles and no lesions could be produced, unless complete obstruction of the blood supply and hemorrhagic infarct occurred. No bloody diarrhea, constipation, or vomiting, as described by Poppe, was observed.

The observation of Holman in a child six years of age in which there was old edema and thickening of the ileum, but no ulcers; and those of surgeons in some cases of acute mesenteric lymphadenitis which showed a diffuse inflammation of the terminal ileum, have led to the belief that there may be a primary lymphatic involvement. This may be progressive, and may open the way for secondary invaders. Also on this hypothesis one can explain the frequent history of a previous appendectomy in cases of regional enteritis, for previous

lymphatic involvement may predispose to the development of acute appendicitis.

Another line of investigation has been with bacillary dysentery. Felsen claimed that he had not seen acute distal ileitis following any disease other than bacillary dysentery. But further work has shown that, while there may be cases of specific ileitis following bacillary dysentery, by far the greatest number of cases do not fall into this category.

Work by Ginzburg and Oppenheimer on involvement of the blood supply has produced nothing new in the knowledge of the etiology of regional enteritis. Likewise, investigation of the appendix as the possible etiologic organ has brought us nowhere. As Bockus so aptly states, "the role of appendicitis in the etiology of terminal ileitis is purely conjectural, and appendiceal inflammation could not conceivably explain the occurrence of enteritis other than that of the terminal ileum."

As a last interesting sidelight, trauma has been accused as a causative agent in compensation courts, but proof of this is lacking and its existence is doubted by Crohn.

When we turn to idiopathic ulcerative colitis we find a disease which, according to Hurst (1921), was first described by Sir William Wilks in 1875. Thus, due to the fact that it is an older disease, much more work has been done in trying to determine its etiology.

We find that ulcerative colitis is world-wide in its distribution. According to most statistics the age of onset is in the second to fourth decades, but it must be remembered that it occurs at any age (Rankin et al.). Again we find that there is no difference in the incidence in the two sexes, and the familial incidence is so low that it is of no importance.

Before considering the etiology we must differentiate between idiopathic ulcerative colitis, and the specific forms of ulcerative colitis. In the latter group fall those cases due to bacillary or amebic dysentery and tuberculous enterocolitis, as well as such systemic diseases as uremia and sickle-cell anemia.

In the former group we find those large series of cases to which no single etiologic agent can be assigned. In these idiopathic cases when we remember the number of systemic reactions, and the appearance of the lesions, we are not surprised that a great deal of work has been done in the field of infection. Work on the dysentery bacilli was done by Felsen, who followed up 122 cases of bacillary dysentery for nine to twelve months and found a total of 10, or 8.2% developing ulcerative colitis. However, Brown and Barger followed 102 cases for sixteen years and had only one case with subsequent development of ulcerative colitis. It has been pointed out that the difference in the age of onset, type of onset and duration, and the lack of infectivity or contagion in ulcerative colitis will differentiate the two.

Although others have said that these differences are more apparent than real, at the present time all that we may say is that chronic bacillary dysentery is identical clinically and pathologically with chronic ulcerative colitis, and that some cases of the latter are an aftermath of an acute bacillary dysentery.

Most physicians are familiar with the work of Bagen (1924) on the diplobacillus. Further work by many others (Paulson, Rafsky et al.) has failed to bring forth any agreement as to an etiologic relationship.

In 1941 Dragstedt, et al. reported on the *Bacterium Necrophorum* with which they had been working for eight years. Attempts to reproduce the lesions of ulcerative colitis in experimental animals by this bacterium and to establish its pathogenicity in man have been unsuccessful, even though in a number of cases in humans this organism has been isolated from the diseased colon.

Almost every organism ever isolated from the feces of patients with ulcerative colitis has been investigated. But, as Bockus has stated about the organisms he has found, outside of increased virulence they were not different from normal bowel inhabitants. A thorough investigation of fungi has also failed to reveal any relationship.

In 1935 Mones and Sanjuan reported their virus theory, believing that the lesions originated in the blood vessels. The primary reaction is in the endothelial cells of the blood vessels, with subsequent emboli formation, extravasation of blood, and final vessel obliteration. However, since bacteria can also produce the lesions experimentally, they had to conclude that some principle is present, giving pathogenic power to normal inhabitants of the bowel. Paulson investigated lymphopathia venerea and was followed by others. The final verdict has been that they are two distinct diseases (Rodaniche et al.).

The other big field of investigation in the etiology of ulcerative colitis has been toward constitutional factors. Metabolic and endocrine influences seem to play a very minor role, if any. Allergy has been accused but, when we remember the conditions as set down by Opie which must be fulfilled before an allergic origin can be established, we must admit that he is still correct in his statement that none have been fulfilled for any infectious disease. These conditions are, "that sensitization precedes the production of the disease by its inciting agent. This inciting agent must be capable of reproducing the disease experimentally in sensitized animals. The inciting agent must be demonstrable in such relation to the human disease that its symptomatology and lesions are explainable." Yet, Andresen has claimed that improvement obtained with exclusion diets has proved an allergic basis of ulcerative colitis in a considerable number of his patients. In this laboratory attempts to produce chronic ulcerative lesions of the small and large intestines of dogs by topic sensitization to foreign proteins and the

use of cathartics have been negative (unpublished results).

The importance of psychogenic factors in the disease are well known, but to say that they are the primary cause seems most improbable. Intestinal juice and enzymes entering the colon in larger amounts than normally, were not found to produce colitis (Portis et al.).

Vitamin deficiencies and deficient diets, such as a high carbohydrate and fat with relatively low vitamins (McCarrison), low Vitamin A (Verder and Petram, and others), or low Vitamin B complex (Langston et al.) have been investigated, but again cannot be ascribed a primary role.

Finally, abnormalities in nervous impulses via the autonomic nervous system were investigated (shock, adrenalin), and it is seen that certain factors affecting the autonomic nervous system may produce colonic changes. But whether these, acting over a long period will result in ulcerative colitis will be seen only by further work. Pitressin and pituitrin produce hemorrhages in the large intestine particularly, but no chronic changes could be produced experimentally (Necheles and Masur).

OUR STATISTICS

In our review we extracted from the files of Michael Reese Hospital a total of 89 cases of regional enteritis and idiopathic ulcerative colitis from the last ten years. Of these, twenty-two were regional enteritis and sixty-seven idiopathic ulcerative colitis.

When we consider the age and sex incidence (Tables I and II) we find that with regional enteritis sixteen of twenty-two cases, or 73%, occurred between the ages of ten and forty; no case below 10 years of age was found, and only 4 cases above 50 years (18%); of this latter group, 3 cases, 14%, were in the age group of 50-60, and only 1 case, 5%, was in the 70-80 year

TABLE I
Age and Sex Distribution of Regional Enteritis
Total, 22 Cases.

Age	-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Male	0	2	2	4	1	1	0	0
Female	0	4	2	2	1	2	0	1
Total	0	6	4	6	2	3	0	1

TABLE 2
Age and Sex Distribution of Idiopathic Ulcerative Colitis
Total, 67 Cases

Age	-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Male	1	7	6	6	14	1	0	0
Female	1	6	8	8	5	1	2	1
Total	2	13	14	14	19	2	2	1

group. When we compare these findings with those of others, quoted above, we see in our group an extension of incidence to the lower age group of 10-19, in which the incidence was the same as in the 20-29 and 30-39 year groups. After 40 years of age, the incidence dropped sharply.

In ulcerative colitis we find the highest incidence of

cases in the 40-49 year group, 27%, and an incidence of 90% of all cases between the ages of 10-49 years. Thus, contrary to the accepted views, in our group of 67 patients, the upper age limit for the greatest incidence of this disease seems to be the fifth rather than the fourth decade.

Our findings as to sex distribution are in accord with those of investigators who did not find a preference of the disease for either sex. In the group with regional enteritis there were ten males and twelve females, and in the group with ulcerative colitis were 35 males and 32 females. Thus, no significant difference as to sex exists in our material.

TABLE 3
Cases Having Both Regional Enteritis and Ulcerative Colitis
Total, 6 Cases

Age	-9	10-19	20-29	30-39
Male	0	1	0	2
Female	0	2	1	0
Total	0	3	1	2

Of the 89 cases, a total of six (Table III) had both, enteritis and colitis, i.e., 7% of the entire group, 27% of the group with regional enteritis, and 9% of the group with ulcerative colitis. This distribution may be interpreted to show, that in primary regional enteritis involvement of the colon may occur more easily than involvement of the small intestine in primary colitis. In this connection it is also interesting, that the age distribution of these 6 cases is of the same order as that found for regional enteritis, 10-40 years, and not like that of ulcerative colitis from below 10 to 50; however, this series is too small to permit definite conclusions on this point.

We then investigated our material, as to appendectomies, to see if any statistical relationship could be drawn (Table IV). A recent study of the incidence of appendectomies among 2,968 students by Stiles and Mulsow, revealed that 297, or 10% had had appendec-

TABLE 4
Incidence of Appendectomy
Total Number of Cases Per Cent of Appendectomies

Disease	Total Number of Cases	Previous	During Disease	None
Regional Enteritis	22	27	55	18
Ulcerative Colitis	67	13	17	70

tomies. These authors then worked out statistically the incidence in the total population of the United States and concluded that 20% of the people have an appendectomy during their lives. Our 27% and 13% in the two diseases do not seem to present significant variants from this figure.

As is seen, our cases were classified as to those having an appendectomy prior to the clinical onset of the disease; those having an appendectomy during the clinical course of the disease; and those having no appendectomy. It is interesting to note in regional enteritis, that of the remaining 73% who had no appendectomy prior to the clinical onset of the disease, 55% had the appendix removed during the disease, as against only 17% in ulcerative colitis. These results compare with those of others. Perhaps this high incidence of appendectomies in regional enteritis can be explained by two factors. (1) The onset of symptoms of regional enteritis often simulates appendicitis, and thus an appendectomy is performed. (2) As stated above, previous lymphatic involvement by acute mesenteric lymphadenitis may predispose to the development of acute appendicitis and thus account for the difference. On the other hand, the diagnosis of appendicitis is not often made during the course of an ulcerative colitis, and a few appendices are removed during surgery for the colitis. Our results seem to exclude the appendix as a portal of entry for an agent which may produce either of the two diseases, although they cannot exclude it with absolute certainty.

CONCLUSIONS

(1) A review of the literature as well as an analysis of 89 cases of regional enteritis and idiopathic ulcerative colitis from the records of Michael Reese Hospital are presented.

(2) In regional enteritis statistics show the greatest age incidence to be between the ages of twenty to forty; our series lowered the age to 10 to 40. In ulcerative colitis statistics place 75% below the age of forty; our series showed the greatest incidence under the age of fifty.

(3) There is no significant sex incidence in the two diseases.

(4) There are a slightly larger number of appendectomies performed before the clinical onset of regional enteritis than that of ulcerative colitis; but a markedly larger number of appendices are removed during the disease in regional enteritis. This can be explained on missed or wrong diagnosis, and actual appendical involvement in certain cases.

We are grateful to the members of our Medical and Surgical Staffs who permitted us the use of their clinical data.

REFERENCES

- Andresen, A. F. R.: Ulcerative Colitis—Allergic Phenomenon. *Am. J. Digest. Dis.* 9:91, 1942.
- Bargen, J. A.: Etiology of Chronic Ulcerative Colitis. *J. A. M. A.* 83:332, 1924.
- Bockus, H. L.: *Gastroenterology* II, pp. 158-196; 549-614.
- Brown, P. W., and Bargen, J. A.: Bacillary Dysentery; Late Results and Relationship to Chronic Ulcerative Colitis. *Am. J. Digest. Dis. and Nutrition* 5:562, 1938.
- Brown, P. W., and Schiefley, C. H.: Chronic Regional Enteritis Occurring in 3 Siblings. *Am. J. Digest. Dis.* 6:257, 1939.
- Clark, R. L., and Dixon, C. F.: Regional Enteritis. *Surgery* 5:277, 1939.
- Crohn, B. B.: Regional Enteritis, Diseases of the Digestive System, edited by Portis. Philadelphia, Lee and Febiger, 1941. pp. 721-729.

8. Crohn, B. B., Ginzburg, L., and Oppenheimer, G. D.: Regional Enteritis. *J. A. M. A.* 99:1323, 1932.
9. Dragstedt, L. R., Dack, G. M., and Kirsner, J. B.: Chronic Ulcerative Colitis; A Summary of Evidence Implicating Bacterium *Necrophorum* as an Etiologic Agent. *Ann. Surg.* 114:653, 1941.
10. Felsen, J.: Relationship of Bacillary Dysentery to Distal Ileitis, Chronic Ulcerative Colitis, and Non-specific Intestinal Granuloma. *Ann. Int. Med.* 10:645, 1936.
11. Ginzburg and Oppenheimer: quoted by Bockus, 3.
12. Hadfield, G.: The Primary Histologic Lesion of Regional Ileitis. *Lancet* 2:773, 1939.
13. Holman, E.: Discussion of Bell, H. G. *California and West. Med.* 41:239, 1934.
14. Homans, J. and Haas, G. M.: Regional Enteritis: A Clinical, Not a Pathological Entity, *New England J. Med.* 209:1315, 1933.
15. Hurst, A. F.: Ulcerative Colitis, *Guy's Hosp. Rep.* 85:317, 1935.
16. Langston, W. C., Darby, W. J., Shukers, C. F., and Day, P. L.: Nutritional Cytopenia (Vitamin M Deficiency) in Monkey. *J. Exper. Med.* 68:923, 1938.
17. McCarrison, R.: Faulty Food in Relation to Gastro-Intestinal Disorder. *J. A. M. A.* 78:1, 1922.
18. Mones and Sanjuan: quoted by Bockus, 3.
19. Necheles, H., and Masur, W.: Gastro-Intestinal Hemorrhages in Dogs from Acetylcholine and Pitressin. *Proc. Am. Physiol. Soc.* p. 500, 1939.
20. Opie, E. L.: The Significance of Allergy in Disease. *Medicine* 15: 489, 1936.
21. Paulson, M.: Present Status of Idiopathic Ulcerative Colitis; With Especial Reference to Etiology. *J. A. M. A.* 101:1687, 1933.
22. Poppe J. K.: Reproduction of Ulcerative Colitis in Dogs. *Arch. Surg.* 43:551, 1941.
23. Portis, S. A., Block, C. L., and Necheles H.: Studies on Ulcerative Colitis and some Biological Effects of Detergents. *Gastroenterology* 3:106, 1944.
24. Rafsky, H. A., and Manheim, P. J.: Significance of Bagen Organism as an Etiologic Factor in Ulcerative Colitis. *Am. J. M. Sc.* 183:252, 1932.
25. Rankin, F. W., Bagen, J. A., and Buie, L. A.: The Colon, Rectum, and Anus. Philadelphia, W. B. Saunders Co., 1932.
26. Reichert, F. L. and Mathes, M. E.: Experimental Lymphedema of the Intestinal Tract and Its Relation to Regional Cicatrizing Enteritis. *Ann. Surg.* 104:601, 1936.
27. Rodaniche, E. C., Kirsner, J. B., and Palmer W. L.: Lymphogranuloma Venereum in Relation to Chronic Ulcerative Colitis. *J. A. M. A.* 115:515, 1940.
28. Sinaiko, E. S. and Necheles, H.: Experiments in Ulcerative Colitis. Failure to Produce it by Lymphatic Mesenteric Obstruction. Surgery, In Press.
29. Stiles, K. A., Mulsow, F. W.: Incidence of Appendicitis from a Survey of College Students. *Am. J. Digest. Dis.* 13:39, 1946.
30. Verder, E., and Petram, E.: Vitamin A Deficiency in the Rhesus Monkey: Studies on Gastrointestinal Tract, Blood and Nervous Symptoms. *J. Infect. Dis.* 60:193, 1937.

Clinical Research

HORACE W. SOPER

ST. LOUIS, MO.

IN recent years since the advent of laboratory research—chemical and bacteriological—our medical journals are filled with long complex articles that rarely have any clinical significance. Before this time epochal advances in medical science were the result of clinical investigation; in fact the history of medicine from the time of Hippocrates until the laboratory era, was a record of clinical research.

In this article I wish to present briefly the results that I have achieved by clinical experience in the 52 years of my practice of medicine.

Chronic Constipation. Many patients endowed with normal colonic mechanism are addicted to the use of purgative drugs and enemas. They should be stopped at once and the fecal column be permitted to form in the lower colon. It will require three or four days' time, when the anal canal sphincter should be dilated. The patient is instructed to attempt defecation after breakfast, before which time he must drink one pint of cold water followed immediately by 15 minutes of active muscular exercises of the abdominal muscles. At the time of defecation he must make *deep intermittent pressure* over the descending iliac and sigmoid flexure with his hands. The diet should be rich in vegetables and fruits; agar-agar and the numerous derivatives of plantago are useful.

Dyspepsia Nervosa. The patient has acquired a habit of belching, the acid contents of the stomach produce an oesophagitis, and a burning sensation results. Belching can be easily controlled by establishing a habit of *deep breathing*. A large number of these cases have

been corrected by teaching them this simple procedure.

Indicanuria. I published my paper on this subject in 1936. Since 1917 I determined that each patient's urine should be examined for indican regardless of the nature of the illness. My conclusions are as follows—only a + plus reaction was considered. "Indican dyscrasia" is the term that should be employed inasmuch as the evidence indicates an inherited tendency. The patient suffers from periodic attacks of migrainous headache with nausea and vomiting. Vertigo and mental sluggishness were frequent complaints, in brief the symptoms usually ascribed to intestinal toxemia or "biliousness." Based upon a study of the dietary habits and food discriminations of such patients I evolved an empiric treatment that has proved to be very beneficial; eggs and rich desserts, particularly egg and milk combinations, are excluded from the dietary. Every two weeks a dose of one or two grains of calomel and soda tablets at bedtime followed in the morning by four to six ounces of Pluto water (which contains both sodium and magnesium sulphate) is administered. Regulation of colonic function, habits, exercise, rest, etc. are valuable adjuncts in treatment.

The Treatment of Hematemesis by the Retention Catheter. This paper was published in 1931. The conclusions are as follows: 1. Immediate gastric lavage removes the blood clots and acid stomach secretion without unduly disturbing the patient, who is free from discomfort, nausea and vomiting. 2. The stomach is kept free from acid contents for a period of three days by continuous siphonage. 3. Recurrent bleeding can be detected at once, and if not checked, early surgical

intervention is advised, late surgery is nearly always a fatal procedure. 4. Blood transfusions and intravenous glucose, 10 per cent solution, in normal saline is employed freely. 5. On the fourth day the tube may be passed through the pylorus and duodenal feeding instituted. 6. The colon can be cleansed of bloody feces and utilized for normal saline proctoclysis.

Sigmoidoscopy. Since 1908 my slogan "that no general examination of a patient is complete without proctosigmoidoscopy" has been followed. 1. The recognition of the rectum and colon as a focus of infection. 2. The removal of polyps by the snare and guillotine, and later in 1930 I published my paper on *Diathermy of the Rectum and Pelvic Colon*, concluding as follows: "Diathermy is the treatment of choice in precancerous polyps, early cancer that projects into the lumen of the gut, and in simple and tuberculous ulcers. 3. Characteristic ulcers can be visualized in every case of early amoebic dysentery; daily examination revealed their quick disappearance by use of one grain of emetin *intravenously* for seven consecutive days. This method of treatment is far superior to the smaller subcutaneous dosage of the drug so frequently erroneously employed.

Pathogenicity of Intestinal Protozoa. In 1943 I concluded my article on the subject as follows: "Intestinal protozoa are pathogenic, producing a low-grade chronic enteritis. In some cases when the host is attacked by an infectious agent, an acute regional ileitis results which is amenable to treatment by the specific drug Stovarsol. If not employed a chronic enteritis occurs which requires surgical intervention."

Chronic Catarrhal Enteritis. Systematic examination of feces establishes the diagnosis; microscopically numerous bacteria and small particles of mucous are found, small "islands" of mucous containing leucocytes, fat globules, striated muscle fibres, and numerous starch granules and particles of cellulose. This condition is noted in every case of achylia gastrica, but is found in many cases with normal HCl in stomach contents. The treatment consists in a high vitamin smooth diet list excluding milk and cream, and the daily administration of one to two drams of brewers' yeast powder.

Brewers' Yeast Powder contains all of the Vitamin B complex, furthermore it continues its fermentative action in the small intestine and facilitates the absorption of all other vitamins and end products of food digestion. It is a splendid nerve tonic and a good adjunct in all forms of anemia.

Synthetic Vitamins. So many patients presented themselves with the remark that "I have taken these Vitamins for one or two years and still suffer from malnutrition"! All that was required to restore them was a diet list of high vitamin content and giving the brewers' yeast, inasmuch as few persons consume enough vitamin B food products. I presented a paper on the subject which concluded that the synthetic vitamins could

not be depended upon. This opinion was later on confirmed by the research work of Prof. A. J. Carlson as well as Prof. Drummond of England.

Treatment of Simple Uncomplicated Peptic Ulcer. In my paper published in 1943 I emphasized that the Sippy method, while giving relief from symptoms, was not curative, the ulcer area being constantly reinfected by the milk bacteria. My treatment consists in feeding evaporated milk and raw egg emulsion with Ralston wheat germ cooked breakfast food, custards and cream vegetable soups, all made from the evaporated milk, gelatins and orange juice with honey. All the essential vitamins are in this list in natural form. The B complex is fortified by brewers' yeast in "00" gelatin capsules. After three to four weeks three meals daily are given, including scraped beef, minced chicken, homogenized canned vegetables and fruits, finally reaching a general diet avoiding roughage, high seasoning and raw or pasteurized milk products. Alkalies are avoided as many patients on the old regimen developed alkalosis. As a laxative, taken early in the morning, I employ a mixture of heavy and light calcined magnesia. The feces of all ulcer patients should be examined frequently for occult blood reaction. If the reaction is constant early malignancy is suspected and surgical exploration is advisable, particularly if the lesion is located on the greater curvature of the stomach.

The Enema. In 1909 I proved by x-ray studies that the employment of the "high enema," using a long rubber tube, was not the correct procedure, inasmuch as the tube coiled up in the ampulla recti, and an enema given by a tube introduced three or four inches would soon reach the caecum. In 1933 in an article on the general employment of the enema I referred to its habitual use in chronic constipation: "It may produce injury to the colonic mucosa, infectious material is likely to be introduced, water and saline solutions are readily absorbed and a toxic solution of fecal matter results." The *Oil Enema* has definite clinical indications. It is given at bedtime with instructions to retain it all night. A 28 F soft rubber urethral catheter to which a glass funnel is attached is introduced four inches into the rectum, and six to eight ounces of the oil is poured in the funnel. The oil soon reaches the caecum and is retained all night. At first I employed cotton seed oil, but found it produced a fatty acid dermatitis in many patients. The mineral oil is not absorbed and furthermore has the great advantage of inhibiting the growth of bacteria, it is not a culture medium. Spastic contractures of the colon, "mucous colitis" and general catarrhal colitis are soon corrected. It is of great value in the treatment of colonic diverticulosis. I have shown x-ray films of complete disappearance of the diverticula in cases in which the entire colon was involved. Finally, the mineral oil enema is the treatment to be advised in all cases of *ulcerative colitis*. It discourages the growth of bacteria, and I have

secured splendid results in a large number of cases; after the ulcers have healed insufflations with air gradually restore the shortened small caliber colon to normal size and function.

Visceral Syphilis. Some years ago I noted the severe liver damage which arsphenamine produced in cases of visceral syphilis. Before the advent of the use of arsenicals in the treatment of syphilis I had secured good results with the oral administration of Bichloride of Mercury and Sodium Iodid. I have resumed this method of treatment with most excellent results. It is far more rational to give it orally where it is quickly and easily absorbed and the dosage can be regulated, than to inject it intramuscularly.

Pernicious Anaemia. Before the advent of Liver Therapy we had no treatment for this disease; since that time I have observed many cases treated both by the ingestion of liver and the extracts orally and by injections. The blood was kept at a high normal level but as time advanced the patients exhibited the symptoms due to atherosclerosis such as coronary arterial disease, Buerger's disease, cerebral hemorrhage, etc. Finally I employed Ventriculin (dried hog's stomach),

HCl, and a diet of low cholesterol and high vitamin content; under this regimen, the patient maintained a good blood picture, and I have had them under observation for many years without the development of the arterial damage so prominent in the group under liver therapy.

Cardiospasm. For many years I have employed the pneumatic balloon dilator in the treatment of this condition; one of the first patients treated by this method could not remain in the city and was permitted to go home after *three consecutive daily treatments*, death soon occurred from perforation peritonitis. I have observed four similar cases treated elsewhere. Since that time I have always allowed seven days to elapse between dilatations. I wish to emphasize that the stretched fibers need that time for readjustment to occur.

In conclusion I wish to express my deep appreciation of the excellent scientific work that is being accomplished in our chemical and bacteriological laboratories, but at the same time to emphasize the fact that there is still opportunity for the clinician to exercise his clinical judgment in diagnosis and treatment.

Regional Ileitis

ISCHIO-RECTAL FISTULA PRECEDING AND FOLLOWING OPERATION FOR ILEITIS

REPORT OF CASE

By

MEYER GOLOB, M.D.*

NEW YORK, N. Y.

No apology need be offered for presenting for publication the case of persistent anal fistula that may be found before and for many years after operation for ileitis. So closely have these ailments been associated that the rectal disturbance from which the patient suffered would, it was assumed, disappear as soon as his ileitis was cleared up, and that his obstinate peri-rectal fistula betrayed a source of infection higher up.

That regional ileitis may be complicated by anal fistula is understandable. Bockus (1) in his recent system of gastroenterology refers to Crohn's thesis that "... fistula-in-ano follows a transportation of infection in the feces to the crypts of Morgani, and is usually preceded by a perianal abscess ... that fistulas in the perianal and perirectal regions are of great importance clinically, since they have been found to precede for years the onset of the characteristic symptoms of ileitis". This implies that although its fountain head of supply is removed and its source of feeding eradicated, distal infection may nevertheless continue un-

interrupted—a situation which casts some uncertainty on the theory that the components in the composite picture under discussion are interdependent.

Association of anal fistula and ileitis, the former emerges from the latter, is understandable; however concomitancy of the two disease entities must also be borne in mind.

CASE

Male, age 41, family history and previous personal history non-contributory. The pertinent facts in the history, physical examination and laboratory work-up are the following: A year and one half prior to his operation in 1937 for regional ileitis he had diarrhea; numbering 5 to 8 movements in 24 hours. These rarely occurred nocturnally. Blood and mucus were seen in the feces. A diagnosis of ulcerative colitis was made, and on further study changed to ileitis. Dr. A. A. Berg's report reads: "Resection of terminal ileum and cecum; ileo-transverse colostomy. Pathological report—Granulomatous-ulcerative ileitis. (Terminal ileitis). Hyperplastic lymphadenitis". The operation was followed by a stormy convalescence and three months in the hospital. Before the operation he had two anal

*Ass't Professor of Gastroenterology, New York Medical College and Flower Hospital.

Submitted June 10, 1946.

fistula. Presumably they must have been considered as the result of ileitis, and the removal of the cause was thought to be assured. The bowel syndrome, and more dominantly the anal fistula which brought the patient to operation, continued postoperatively and were manifest when he was examined by the writer in May 1944.

It is to be noted that these fistula, with a third additional one, are active, (exuding material) or inactive, depending upon the consistency of the stool; exuding when the movements are diarrheal, and non-active when the stool is well formed. Curiously, the diarrheal episodes occurred on the day of rest.

The physical findings were essentially negative except for rectal fistula, blind internally and confined to left lower quadrant of the perianal region, angry in appearance and very sensitive to touch.

Laboratory data: Blood cytology and erythrocyte sedimentation rate were normal. Gastric chemistry revealed normal acid values. Feces under food control was negative for occult blood.

Sigmoidoscopy: Instrument met resistance at 15 cm. from the anal ring and no departure from the normal was noted.

Roentgenologic survey of the gastrointestinal canal (progress meal) with hourly observation of the small bowel revealed no defects in the mucosal pattern.

Colon suspension enema showed no variation from the normal. The operation for the ileitis was evident. No tender areas were found. In the region of the colon anastomosis, some narrowing of part of the terminal ileum was noted, but it dilated as evidenced by the double contrast x-ray film. Incidentally, no pain was caused by air inflation. It was this procedure which accounted for the disparity in the two colon suspension enema studies. The narrowing at the anastomatic area was interpreted as a recurrence for which operation was advised, so that the fistulous tract of the persistent perianal abscess would heal before the pelvis is damaged.

Note: Three points in the history of this case merit comment:

1. If fistulization in the perianal region was a phase of the ileitis, the removal of the primary lesion was not rewarded with a cure of the multiple rectal fistula. It is assumed that skip areas proximal to the lesion were searched for operatively and not found, so that there were no diseased areas left to transmit infection to the anal region. Had the fistula in-ano healed spontaneously following the ileo-transverse colostomy, the occurrence of regional ileitis with distal infection, (the latter dependent on the former), would have corroborated the preoperative diagnosis with respect to the rectal condition. Felsen (2) refers to several cases of chronic ulcerative colitis complicated with ischio-rectal abscesses which cleared up with subsidence of intestinal infection. He also points to a case of

distal ileitis where a large abscess was present between coils of ileum and mesentery and which finally broke through the anterior abdominal wall; and a case in which, "the abscess burrowed downwards beneath poupart's ligament to appear on the inner aspect of the right, where eventually a fecal fistula formed that was connected directly with the distal portion of the ileum". However, the diagnosis of regional ileitis with ischio-rectal pathology as a complication is now disconcerting, in view of the persistence of the latter long before operative intervention and for many years after. Under such circumstances, it seems logical to assume their complete separation into distinct but concurrent sites of pathology.

2. The diarrheal episodes occurred on his day of rest, and continue to do so now, many years after the operation. Surely, an anatomic cause is not too selective of the activity or inactivity of the host. No diarrhea occurred nocturnally. According to the patient's own observation, the number of bowel movements varied with his emotional environment, and were far more dominant when he was at home than at work.

3. From a roentgenologic standpoint, as mentioned previously, a diagnosis of recurrent ileitis is not persuasive, since the area that appeared narrowed has dilated to a normal calibre with the double contrast enema.

It was the writer's opinion (May 1944) that the removal of the fistula was indicated regardless of its relationship to the ileitis, but that the relationship was most unlikely. The bowel syndrome for which this case was operated upon in 1937 and which persisted in a non-persuasive clinical pattern of regional ileitis should now be regarded as a functional, intestinal aberration such as colon instability.

PROGRESS OF CASE

June 1945, Dr. Charles Gordon Heyd admitted this patient to the New York Postgraduate Hospital. Diagnosis: Ischio-rectal fistula, Communicating Multiple. Operative findings: ". . . there are three external orifices, approximately at five o'clock, three o'clock and one o'clock on the watch dial and distant about three cm. from the anal orifice. These communicate with one another and apparently had their origin approximately two and a half inches in the patient's left rectal lateral wall. The operation consisted of a probing of the three orifices and establishing a common communicating track. All of the overlying tissue was then resected, and the wound curreted . . ."

REPORT ON EXAMINATION OF TISSUE

Pathologist, Dr. W. N. Richter.

Microscopic: Section reveals anal tissue. The surface of two particles is replaced by vascular granulation tissue in which are islands and short lacunae of epithelial tissue. The granulation tissue is studded with

lymphocytes, plasma cells and occasional leucocytes. There are a few dispersed areas of degeneration and hemorrhage within the granulation tissue. Diagnosis: Fistula in-ano.

Dr. Heyd was questioned in retrospect, on consideration of the clinical impression and the operative findings and the expected favorable outcome, whether he thought that the anal fistulization in this case was in any way related to the ileal lesion for which the patient was operated upon in 1937. To this question, Dr. Heyd replied: "I am of the opinion that the ischio-rectal fistula of Mr. N. L. are in no way connected with his ileitis. I think they are separate and distinct, and I believe he will have a very good result".

At this writing, one year after the operation, the patient is noncomplaining and emotionally at ease, as the following lines from him attest: "Just a few words to let you know that I am feeling fine and have gained about ten pounds since I was operated upon by Dr. Heyd. I have had very little trouble with my rectum since the fistulas were removed. My movements vary from two to four times daily. My stool is much more formed than it used to be. On the whole I would say that by removing the fistulas my entire condition was helped".

Comment:—

With respect to his bowel syndrome, enough residue is left to preclude the claim of complete return to normality. Brown and Donald (3) state that approximately three-fourths of the patients who have undergone ileocolostomy complained of postoperative diarrhea, and that resection of a diseased segment of the small intestine, with entero-anastomosis, usually is not followed by post-operative diarrhea. Therefore, they argue, that "either loss of the ileocecal normal junction or, more likely, loss of the liquid absorbing portion of the right colon, is the reason for post-operative diarrhea." It is apparent that post-operative diarrhea, while it may indicate a recurrence of the enteritis, may also betray a physiologic aberration as the result of the operation. Colon instability as part of the patient's emotional mark of identification, might also be held accountable for the bowel condition.

DISCUSSION

It is not within the scope of this paper to enter into a lengthy discussion of the disease designated ileitis. But for the purpose of clarification and analysis, a report of some of the salient features of the disease is pertinent. This case illustrates the fallacy of relying exclusively on the removal of the primary source, in expectation of a spontaneous cure of the rectal condition. The two conditions, related or unrelated, could have been operated upon simultaneously or consecutively as though they were distinct entities. Wilensky and Moschcowitz (4) in 1923 reported four cases of non-

specific granuloma of the intestine, where the lesion seemed restricted to the ileum and cecum. In 1932 the writer (5) reported a case then designated as infectious granuloma of the intestine. These few case reports in the medical literature were presentations of many cases identified as non-specific inflammatory tumors of the gastrointestinal canal. These cases presented diagnostic difficulties for what is now patent diagnosis—the existence of a well established clinical entity. The writer's case resembled a malignant neoplasm, not only clinically but roentgenologically as well. The presence of enlarged neighboring glands reinforced the deceptive picture. The resected section and histopathology yielded evidence of chronic infectious granuloma.

Although regional ileitis may simulate ulcerative colitis in clinical features there is one manifestation which is distinctly characteristic of each. Thus, while colitis does not transpass into the ileum except for a late complication of progressive pathology, a terminal ileitis, as it advances, invades the colon—enterocolitis being the result of an evolutionary process, with the primary focus in the small bowel. This is in agreement with Felsen's concept, expressed in 1932 and now generally accepted, that "distal ileitis may extend beyond the ileocecal valve into the colon". In distinguishing between an ulcerative colitis that invades the ileum and the reverse case of the ileum transpassing into the colon, pathologists point out that in colitis, the ileum is thin walled and dilated, the fistula are not seen, and sidetracking does not cure; while in regional ileitis, the ileum is thickened and stenosed, fistula occur in 50% of the cases, and sidetracking usually heals the lesion. Clinically, positive sigmoidoscopy and roentgen evidence of structural disease affirm ulcerative colitis and negate regional ileitis.

Reverting to the case under discussion, recurrent ileitis was definitely contradicted by the clinical picture. The lesion was extirpated in 1937 with good result except for the fistula in-ano. This would argue favorably that the rectal condition was an attendant circumstance to a diseased ileum.

TERMINOLOGY

From the standpoint of definition, ileitis is a subacute or chronic granulomatous, non-specific inflammatory process, commonly involving the terminal ileum, but occasionally affecting the proximal ileum. Formerly it was thought that the granulomatous lesion of the intestine was limited to the terminal ileum, ending abruptly in the ileo-cecal valve. It has since been found however, that the condition may infiltrate not only the terminal segment, but any part of the ileum and even the jejunum. The term "regional ileitis" therefore has been adopted in preference to "terminal ileitis". The

disease has also been designated under the descriptive term, cicatrizing enteritis, regional enteritis, chronic ulcerative enteritis and non-specific granuloma of the intestine. The latter term, I believe is all comprehensive. As Wilensky (6) pointedly writes, the terminology "... indicates the nonspecificity of the lesion, and determines the lesion as an inflammatory, and not as a neoplastic phenomenon".

The clinical bizarreness of this condition, aggravated by its localization in the right iliac fossa where mimesis is prevalent, gave rise to a confusion of terminology which did not come to an end until medical attention was so ably directed to it by Crohn and his colleagues.

In passing, it may be pointed out that the case under discussion gives demonstration of the fact that toxicity and pathology are not necessarily parallel; for otherwise, the long delay between the ileitis and rectal operations could hardly be accounted for. That an ischio-rectal abscess may result from infection spreading by lymphatic extension, is conceivable; but on eradication of the source, complete or at least partial subsidence of the rectal condition should have occurred. Since the latter preceded the clinical picture of ileitis by a relatively long time, we have weighty support for the contention that the two conditions must have a separate basis. According to Buie (7) perianal abscess is the third stage in the pathology. The first stage begins with involvement of the anal crypt and the extension of the fistula into the adjacent structures, where it enters the second phase, during which the infection extends in various directions. Buie questions, "Whence comes the infection to which the onset of the disease is due, and through what portal of entry does it gain admission to those structures which firmly break down into an abscess and ultimately suffer the development of a fistulous tract?". He points out that "Any of the pyogenic organisms which inhabit the colon are capable, on gaining admission to normal tissues, of producing inflammatory changes which may terminate with the formation of an abscess." As to the nature of the infection, Buie avers that tuberculosis may be associated with anal fistulas; but, he makes no mention of

it at least in some of the cases of regional ileitis, as either preceding or following pathology in the ileocecal region.

A search of current literature in support of rectal fistula preceding ileitis disclosed eleven cases of "Cicatrizing Enteritis" reported by Cutler (8) in only one of which an ischio-rectal abscess developed. But the ischio-rectal fistulous tract excized proved tuberculous. Cutler asserts "Because of proved tuberculosis of the fistula and the fact that tubercle bacilli were said to have been found in the stool on occasions, and because the appendix was thought to be tuberculous, the diagnosis of cecal tuberculosis was made". The patient was explored: Histologic report: Cicatrizing enteritis, not tuberculosis". I cite this case to direct attention to concomitancy of divergent entities, the same as in the writer's case, except for non-specific cause of the ischio-rectal abscess. Had the rectal condition been recognized as local and not believed to be fed from higher up, we would have been spared the dismal clinical picture of psychic trauma that effected and built up in the patient an anxiety state, surcharged with depression of spirit—a classic example of a psychosomatic problem. At this writing, reassurance and the return of self confidence stand out in bold relief against the erstwhile anxiety neurosis. One recalls from general practice the numerous cases of ischio-rectal abscesses definitely unrelated to other conditions; in the case presented, it was merely an instance of concurrency.

Beginning with the cellularity of intestinal granuloma as established by earlier writers and later buttressed by further pathological investigations, clinical implications and operative findings, Crohn succeeded in building up a clinical concept of ileitis which has the merit of being both informative and comprehensible. However, despite dependable criteria for the identification of this disease, each case of regional ileitis calls for individualization, for a more accurate analysis of symptoms, and physical findings whether related or not to the primary lesion, and for a clear understanding of the all embracing concept of a disease entity.

REFERENCES

1. Bockus: *Gastroenterology*, Vol. 11, Saunders.
2. Felsen: *Bacillary Dysentery, Colitis, Enteritis*, Saunders.
3. Brown, W. and Donald, C. J.: *Prognosis of Regional Enteritis*, *Am. J. Dig. Dis.*, Vol. 3:87, 1942.
4. Moschowitz, E. and Wilensky, A. O.: *Nonspecific Granuloma of the Intestines*, *Am. J. M. Sc.*, 166:48, 1923.
5. Golob, M.: *Infectious Granuloma of the Intestines*, *Med. Jour. and Record*, April 20, 1932.
6. Wilensky, A. O.: *The Essential Nature of Nonspecific Granulomatous Lesions of the Gastrointestinal Tract*, *Surgery*, August, 1939, Vol. 6, No. 2.
7. Buie, L. A.: *A Consideration of the Terminology and Management of Anal Fistulas*, *The Southern Surgeon*, May, 1940, Vol. IX, No. 5, pp. 351-259.
8. Cutler, E. C.: *A Neglected Entity in Abdominal Pain and a Common Disease—Cicatrizing Enteritis*, *N. Y. State J. M.* Feb. 15, 1939.

Amoebiasis: The Role Of Bacteria In Symptomatology

- I: SIGMOIDOSCOPIC FINDINGS IN SYMPTOMATIC AND ASYMPTOMATIC CASES
II: THE EFFECT OF SULFADIAZINE ON SYMPTOMS AND SIGMOIDOSCOPIC FINDINGS

MAX ELLENBERG

Lt. Col., Medical Corps.

NEW YORK, N. Y.

THE problem of the relationship of the asymptomatic carriers and the symptomatic cases has long been prominent in the field of amoebiasis. No satisfactory explanation has been forthcoming, as yet, to account for the co-existence of these two categories.

Recent thought has been in the direction of establishing a clinical relationship between the two groups. Craig (1) maintains that most "carriers", if carefully evaluated, have some symptoms or signs. In a recent study (2), 833 cases of amoebiasis were reviewed. In that series, a comparison of the symptoms, physical signs, and laboratory examinations revealed an identity in pattern of symptomatic and asymptomatic cases. From this it was inferred that specific pathological changes must be present in both groups.

Nevertheless, in spite of the analogies, the fact that there is a marked discrepancy in frequency and severity of symptoms between the two categories remains unexplained. Attempts have been made to account for this difference on the basis of (a) variations in strain virulence, and (b) the possibility of *E. Histolytica* being a facultative, rather than obligatory tissue invader dwelling in the intestinal lumen.

(a) Virulence of strains of *E. Histolytica*. There is little doubt that difference in some strains of *E. Histolytica* do exist. (3) On the other hand, all endeavours to demonstrate a greater potency in strains from symptomatic cases have been futile, and have uniformly revealed a nondifferentiable pathogenicity between strains from symptomatic and asymptomatic cases. Kessel (4) infected kittens with *E. Histolytica* obtained from carriers as readily as with those obtained from cases of acute amoebic dysentery; further, the incubation periods, incidence of spontaneous recovery and average length of life in fatal cases did not vary in these groups. Hegner et al (5) had the same experience in monkeys. Walker and Sellards (6) obtained positive results by feeding cysts from "carriers". Other reports with similar conclusions are available.

(b) Obligatory parasitism. If it could be shown that the *E. Histolytica* may exist as a lumen contaminant, a satisfactory explanation would be had. Post-mortem examinations have been very impressive in disproving this. Dock (7), Musgrave (8), Bartlett (9), Hiyeda and Suzuki (10), and Faust (11), all demonstrated specific lesions attributable to and containing the *E. Histolytica*

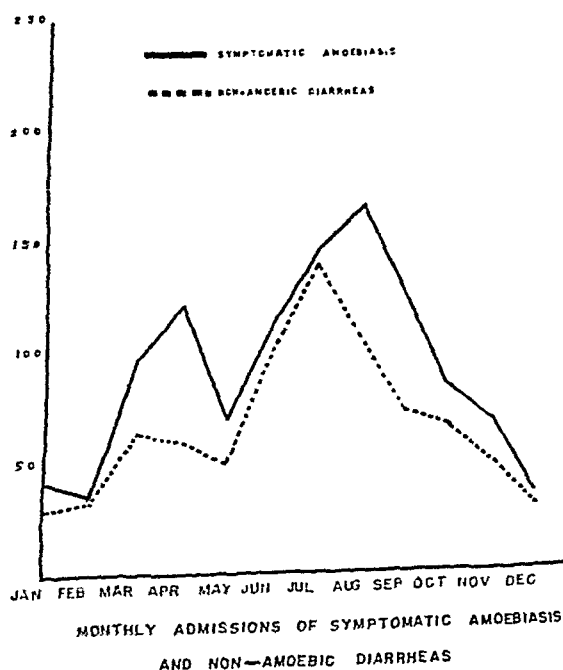
in patients who had died from causes other than amoebiasis, and in whom amoebiasis was not suspected during life. Comparable observations have been made in asymptomatic, naturally infected monkeys (12). The evidence indicates that *E. Histolytica* is an obligatory parasite rather than a facultative or accidental tissue invader.

In approaching the problem of determining the variant or variants producing these two categories, an evaluation of accumulated data, experiences, and observations offered a lead:

(1) The simultaneous endemicity of non-specific diarrheas wherever symptomatic amoebiasis is prevalent is well known. Equally familiar is the relationship in rate of occurrence of these two groups of intestinal affections to climatic variations. Our own experience confirms this, (Chart I). The parallelism of admissions to this hospital of symptomatic amoebiasis and non-amoebic diarrheas during a twelve month period is obvious.

(2) Although the occurrence of symptomatic amoebiasis varied with meteorological influences, routine stool surveys yielded a relatively constant per-

CHART I



centage of positive asymptomatic cases throughout a twelve month period.

(3) The diarrheas encountered were clinically non-differentiable as to etiology. This has been previously pointed out by many authors.

(4) Some of our asymptomatic cases, diagnosed by routine stool surveys, delayed hospitalization because of mitigating military circumstances. Several of these suddenly became symptomatic, as though a trigger mechanism had been released.

(5) In an earlier (unpublished) attempt to determine the effectiveness of penicillin in eradicating the *E. Histolytica*, it was observed that marked symptomatic relief was obtained whereas the *E. Histolytica* persisted in the stools.

(6) Many of our cases of amoebiasis gave a history of previous bouts of diarrhea that had been successfully treated with sulfa drugs without benefit of stool examination.

All these facts seemed to include the possibility that bacteria might be a determining factor in upsetting the host-parasite equilibrium which exists in the asymptomatic cases. Hence, this investigation was conducted in an attempt to evaluate the relative importance of bacteria in amoebic infection.

Two approaches were employed. In the first, sigmoidoscopic examinations were done prior to any therapy in symptomatic and asymptomatic cases. Secondly, the effects of sulfadiazine on the symptoms and sigmoidoscopic pictures were observed.

All the patients in this report were American army personnel admitted to an Army General Hospital located in Calcutta, India. It is to be pointed out that our cases were seen early in the course of the disease.

I: SIGMOIDOSCOPIC FINDINGS IN SYMPTOMATIC AND ASYMPTOMATIC CASES

Sigmoidoscopic examinations were performed on unselected cases of proven amoebiasis. Of the 176 cases in this series, 107 were symptomatic, and 69 were in the asymptomatic category. The findings were analyzed as to frequency of presence of lesions, specificity of the observed abnormalities, and concomitant features.

DESCRIPTION OF THE LESIONS

The observed abnormalities can be grouped into the following categories: 1. amoebic lesions; 1a. those amoebic lesions, included in (1), that showed the presence of bacterial or inflammatory components; and 2, bacterial lesions.

1. Amoebic Lesions:

The distribution of the specific amoebic lesions was characterized by a predilection for the valves; on the valves, the preponderance of findings was on or near the free margin. However, the involvement was not confined to these anatomical structures. Minute pin-

point ulcerations were by far the most frequent type of lesion; next in frequency were yellowish sub-mucosal elevations; least common and present in only 9 (5%) of the 176 cases were the classical, text-book lesions of amoebiasis—the punched-out, deep ulcer with undermined margins. No one type of lesion was present alone necessarily, but one type always predominated in any individual case. Aside from the infrequency of the classical amoebic ulcerations, the nature of the findings are in general agreement with previous reports (13), (14). This discrepancy is best accounted for by re-emphasizing that our cases were seen early in the course of the disease.

1a. Bacterial or Inflammatory Component of Amoebic Lesions:

This aspect is to be stressed because of its interpreted implications. An inflammatory or bacterial component of specific amoebic lesions was determined by (a) the presence of an erythematous areola surrounding the pin-point ulcerations, or the yellowish elevations; (b) the presence of a grey, necrotic inflammatory slough or membrane overlying an ulcer, the ulcer in such cases being invariably surrounded by an erythematous margin; (c) the presence of generalized erythema and edema of the mucosa in the presence of amoebic lesions. Such accompaniments have been previously observed and described, but heretofore have been accepted as an inherent part of the sigmoidoscopic picture in amoebiasis. The reasons for considering these as distinct bacterial or inflammatory components will become more evident in the succeeding part of this report. It will suffice to mention at this juncture that pathologically, the uncomplicated specific amoebic intestinal lesion does not call forth an inflammatory response.

2. Bacterial Lesions:

In several instances, the sigmoidoscopic picture was that of a pure bacterial infection and consisted of generalized edema and erythema of the visualized mucosa. Occasionally, there were accompanying areas of superficial, grey, necrotic slough, interspersed with petechial and submucous hemorrhages.

ANALYSIS OF FINDINGS

Table I represents the number of cases each, of specific amoebic lesions, pure bacterial pictures, and normal sigmoidoscopies in the 107 symptomatic and 69 asymptomatic cases examined. It is evident that the occurrence of sigmoidoscopically visible amoebic lesions is virtually identical in the two groups—73% of the symptomatic cases and 68% of the asymptomatics. A pure bacterial picture was observed in 12 symptomatic cases, and in only 3 asymptomatic cases.

	107 Symptomatic Cases	69 Asymptomatic Cases
Specific Amoebic lesions	78 (73%)	47 (68%)
Pure bacterial lesions	12	3
Normal	17	19

Table I: Incidence and Nature of Sigmoidoscopic Findings

Table II represents the number of cases with bacterial components of specific amoebic lesions, and the number of uncomplicated cases. Of the 72 symptomatic cases with specific amoebic lesions, 56, or 78%, showed the presence of a bacterial component. Only 9, or 19%, of the 47 asymptomatic cases with amoebic lesions had a similar bacterial component. The marked disproportion is apparent.

COMMENT

The demonstration of the equivalent incidence of amoebic lesions in symptomatic and asymptomatic cases adds another link in establishing their fundamental sameness. One can justifiably state that in view of the identical pattern of symptoms, signs, and laboratory findings, (2), and now the pathological identity, that *E. Histolytica* produces the same disease pattern regardless of the symptomatic picture. The frequent presence of a bacterial component of the lesions in symptomatics and the relative absence of such involvement in the asymptomatics accentuates this finding as a sharp differential feature between the two. The relationship of this feature to the differences in degree and severity of the clinical manifestations is dealt with in the subsequent part of this report.

	Symptomatic Cases	Asymptomatic Cases
Specific Amoebic lesions	78	47
Bacterial Components	56 (78%)	4 (19%)

Table II: Incidence of Bacterial Components of Amoebic Lesions

SUMMARY

(1) Specific amoebic lesions were observed in 73% of 107 symptomatic cases and in 68% of 69 asymptomatic cases.

(2) Bacterial or inflammatory components were present in 78% of amoebic lesions in the symptomatic cases, whereas only 19% of the asymptomatic cases presented this finding.

(3) The amoebic lesions were chiefly pin-point ulcerations and yellowish, raised submucosal elevations.

(4) The relative infrequency of the classical punched-out amoebic ulceration is noted.

II: THE EFFECT OF SULFADIAZINE ON THE SYMPTOMS AND SIGMOIDOSCOPIC FINDINGS

59 unselected cases of amoebiasis were handled in the following manner:

(1) A sigmoidoscopic examination was performed prior to instituting any therapy.

(2) The *E. Histolytica* was demonstrated in the stools, or on scrapings from visualized lesions, in every instance before administering medication.

(3) Sulfadiazine was then given commencing with an initial dose of 2 grams followed by 1 gram every four hours day and night for three days; the dosage was then reduced to 1 gram every six hours day and night for two days. The total amount used was 27

grams in a five day period. Equal doses of sodium bicarbonate were given.

(4) In 53 of the 59 cases, a second sigmoidoscopic examination was done at the conclusion of sulfadiazine treatment. A swab of the lesions was taken for direct examination and further stool studies were made.

(5) The symptoms and sigmoidoscopic pictures were analyzed before and after treatment.

RESULTS

(a) Symptoms.

The effect of sulfadiazine on symptoms in this series is shown in Table III. Of the 59 treated cases, 41 were completely cleared of symptoms, and 17 were considerably alleviated. One patient failed to show any favorable response. Thus 98% of the entire series were rendered either completely symptom free or manifested definite improvement. No cases were aggravated by the sulfa drug.

All symptoms (e.g. diarrhea, constipation, cramps, anorexia, nausea, distension, flatulence, etc.) responded in equal degree.

Total number of Cases:	59
Completely Cleared :	41 (69%)
Improved :	17 (29%)
Failure :	1 (2%)

Table III: Effect of Sulfadiazine on Symptoms

Type of Lesion	Number	Effects of Sulfadiazine		
		Cleared	Improved	Unchanged
Bacterial Component (of Amoebic Lesions) :	38	25	10	3
Pure Amoebic :	11	0	0	11
Pure Bacterial :	3	1	2	0
Normal :	1	0	0	1

Table IV: Effects of Sulfadiazine on Sigmoidoscopic Findings in 53 Cases

(b) Sigmoidoscopic Findings.

Table IV shows the distribution of lesions before and after treatment with sulfadiazine. In 38 cases showing bacterial components of amoebic lesions 35, or 92%, showed complete clearing or definite improvement of the accompanying inflammations. The amoebic lesions, per se, were completely unaffected; indeed they often became more distinct and were more clearly visualized and identified as the accompanying inflammation receded.

The changes observed were of the following nature: diffuse inflammatory involvement subsided; grey, necrotic sloughs or membranes on the surface of large ulcers disappeared, leaving a clean-based ulcer devoid of an erythematous margin; the inflammatory areolas surrounding the pin-point ulcerations and the yellow sub-mucosal elevations were no longer visible; friability decreased; petechial and submucous hemorrhages decreased.

Of the 3 cases with pure bacterial proctitis, one cleared completely, and two showed distinct improvement.

11 cases were originally found to have lesions charac-

teristically amoebic in origin without bacterial components. All of these were found to persist entirely unaffected by the sulfa drug. Nevertheless, in spite of the inability to visualize any change, the symptoms in these cases were alleviated in the same measure as in the other cases. It should be borne in mind that only one segment of the large bowel is visualized, and one can only surmise as to the nature and extent of lesions in the non-visualized intestine.

(c) Swab and Stool Examinations.

To ascertain whether the beneficial effects of the drug were a result of direct action on the *E. Histolytica*, swabs and scrapings were taken from lesions visualized at the second sigmoidoscopic examination. Repeat stool studies were also performed. *E. Histolytica* was demonstrated, in the stool or swab, in every case even though the symptoms had cleared and the sigmoidoscopic picture had measurably improved. No morphological changes were detectable in the *E. Histolytica*.

PENICILLIN

In 4 cases, penicillin (30,000 units intramuscularly every three hours for four days) was used. Symptoms were considerably improved in 3 of these 4 cases, whereas one failed to show any response. Sigmoidoscopic improvement, in that the bacterial component cleared, was observed in all 4 instances. The number of cases is far too small to permit of any conclusions. It was our general impression that the effects were not quite as dramatic as with sulfadiazine, nor did it seem to be as efficacious.

The series did not include any cases simultaneously treated with penicillin and sulfadiazine.

SUMMARY

(1) 98% of 59 cases of amoebiasis were either cleared of symptoms or markedly improved following the use of sulfadiazine.

(2) All symptoms responded in equal degree.

(3) 92% of cases having amoebic lesions with an accompanying inflammatory component showed distinct clearing of the inflammation after the use of sulfadiazine.

(4) Specific amoebic lesions showed no response to sulfadiazine.

(5) The beneficial effects of sulfadiazine were not related to any action on the *E. Histolytica*.

DISCUSSION

The sigmoidoscopic findings as presented indicate that the basic pathology and incidence thereof from the viewpoint of *E. Histolytica* infection is essentially identical in symptomatic and asymptomatic cases. The presence of an inflammatory component of the lesions in the symptomatic group, the symptomatic and sigmoidoscopic response to sulfadiazine and penicillin, and the persistence of *E. Histolytica* and specific

amoebic lesions following such therapy, permit the hypothesis that the relative host-pathogen equilibrium that exists in the asymptomatic phases of amoebiasis is upset by secondary bacterial pathogens.

There are many observations in the literature in keeping with this interpretation of the observations. In discussing the pathology of intestinal amoebiasis, Mansohn-Bahr (13) states: "At first there is little or no response on the part of the host, but when bacteria gain entrance to the tissues, marked cellular reaction occurs and the submucosal lesion takes on the appearance of a pyogenic abscess". Meleney (15) made a similar observation. Reese (16), working with kittens, found it impossible to discriminate between the results of bacterial and amoebic activities in the pathological lesions. Craig (1) remarks that it is undoubtedly true that there is no such thing as a pure amoebic infection, for every infection is complicated by the presence of bacteria, often pathogenic, which have entered the tissues through lesions produced by the amoebae. A marked influence of pathogenic bacteria on the incidence and extent of pathological lesions in the intestines of kittens was found by Spector (17). Cleveland and Sanders (18), in a convincing series of experiments, demonstrated the relationship and importance of pathogenic bacteria to *E. Histolytica* in the production of liver abscesses in cats.

Clinically, the therapeutic value of anti-bacterial drugs in chronic recurrent, refractory cases of amoebiasis has recently been demonstrated by Hargreaves (19). The simultaneous use of penicillin and sulphasuxidine in 47 severe refractory cases produced rapid symptomatic relief, sigmoidoscopic improvement and subsequent clearing of the *E. Histolytica* with specific anti-amoebic drugs even though these same drugs had previously failed. He concluded that secondary bacterial infection is an important factor in chronic cases which have proved refractory to specific treatment.

The concept that secondary invasion by bacterial pathogens of amoebic ulcerations is a determining factor in symptomatology accounts for many of the phenomena observed in *E. Histolytica* infection. It readily explains the co-existence of asymptomatic and symptomatic groups, as well as the transition from the asymptomatic phase to the clinically manifest picture. Because of a mutual dependence on bacterial pathogens, there is a seasonal variation in the incidence of symptomatic amoebiasis in the same ratio as non-amoebic acute enteric disorders, whereas climatic factors have little influence on the incidence of asymptomatic cases. The clinical non-specificity of diarrhea associated with *E. Histolytica* infection becomes understandable. And, of course, it readily accounts for the response of symptoms and sigmoidoscopic changes following the use of anti-bacterial drugs.

Unfortunately, because of inadequate technical and laboratory facilities, an extensive bacteriological study

of the stools was not done. Such investigation is indicated; but from clinical observations, and on the basis of experimental results in the literature, one could confidently predict that no one specific bacteria was implicated, but that many different pathogens are responsible.

One might hypothesize as to the series of events that take place in the pathogenesis of the clinical and pathological picture in amoebiasis:

- (1) *E. Histolytica* is ingested.
- (2) By virtue of its cytolytic and toxic properties, and its invasive propensities (possibly in association with bacteria), it produces necrosis and erosion of the intestinal mucous membrane. At this stage, the patient is essentially "asymptomatic".
- (3) The ulcerations are secondarily invaded by bacterial pathogens with the production of the symptomatic aspect of the disease. The severity of the clinical picture would then depend on the nature and virulence of the invading organism or organisms.
- (4) Concomitant extension of the ulcerative process takes place, the ulcers becoming larger and extending more deeply into the intestinal wall.
- (5) With each re-invasion there is an exacerbation of symptoms; the ulcers become more chronic, the fibrotic changes more dominant, and the entire picture becomes progressively irreversible. Eventually the picture of severe, chronic amoebic dysentery is the end result. At this stage, even elimination of *E. Histolytica* still leaves a scarred, mutilated bowel with permanent interference of normal physiology.

There is no intent to deprecate the pathogenicity of *E. Histolytica* or to minimize the potential malevolent effects of its presence in the intestinal tract. This has been too well demonstrated beyond reasonable doubt. Further, the response of symptoms and intestinal pathology to drugs that have been proven to be specific for *E. Histolytica* has been thoroughly demonstrated. The beneficial influence of either anti-amoebic

or anti-bacterial drugs on the findings strongly suggests a symbiotic relationship between *E. Histolytica* and bacteria. It would appear that *E. Histolytica* is essential in the production of basic pathological lesions, but that the presence of bacteria is a determining factor in the production of the clinical picture.

It cannot be stated with certainty that bacteria constitute the sole determining factor that governs the host-parasite equilibrium in *E. Histolytica* infection. There may or may not be other agents. However, it is clear that bacteria are at least a most important element.

The influence that these observations will have on the future approach to amoebiasis remains to be evaluated, and is beyond the scope of this paper. However, some speculative possibilities of application are worthy of note. (1) The therapy of amoebiasis relies heavily on drugs possessing severe toxic properties. Mention has already been made of the excellent results attending the use of anti-bacterial drugs in the treatment of severe, chronic, recurrent amoebic dysentery. The adjuvant use of such drugs may prove feasible in early cases as well, with subsequent reduction in dosage, or even elimination of some of the more toxic anti-amoebic drugs. (2) The question of the importance of bacteria in the genesis of complications of amoebiasis is raised. Evidence suggesting this is not lacking in the literature. The possibility of prevention, and therapy in the formative stages of these complications calls for further study. (3) The use of anti-bacterial drugs as a prophylactic measure for travelers and troops exposed to *E. Histolytica* and who lack facilities for fundamental sanitary precautions may prove a fertile field of investigation.

CONCLUSION

1. The basic pathological pattern is identical in symptomatic and asymptomatic cases of *E. Histolytica* infection.
2. The secondary invasion of amoebic ulcerations by bacterial pathogens is a decisive determinant in the symptomatology of amoebiasis.

REFERENCES

1. Craig, C. F.: Etiology, Diagnosis, and Treatment of Amebiasis, 1944, Baltimore.
2. Ellenberg, M., Peyton, J. H., Gilmore, J. T., and Klein, S.: Amoebiasis: Observations in 833 Cases to be Published.
3. Meleney, H. E. and Frye, W. W.: Further Observation on the Pathogenicity of Certain Strains of *E. Histolytica* for Kittens. *Am. J. Hyg.* 24:414, 1936.
4. Kessel, J. F.: Amoebiasis in Kittens Infected with Amoebae from Acute and "Carrier" Human Cases. *Am. J. Hyg.* 8:311, 1928.
5. Hegner, R., Johnson, E. M., and Stabler, R. M.: Host-Parasite Relations in Experimental Amoebiasis in Monkeys in Panama. *Am. J. Hyg.* 15:394, 1932.
6. Walker and Sellards, 1913. Quoted by Craig (1).
7. Dock, G.: Observations on the Amoeba Coli in Dysentery and Abscess of the Liver. *Texas Med. J.* 6:419, 1891.
8. Musgrave, W. E.: Intestinal Amoebiasis without Diarrhea; A Study of 50 Fatal Cases. *Philip J. Sci. (B)* 5:229, 1910.
9. Bartlett, G. B.: Pathology of Dysentery in the Mediterranean Expeditionary Force, 1915. *Quart. J. Med.* 10:185, 1917.
10. Hiyeda, K. and Suzuki, M.: Pathologic Studies of Human Amoebic Ulcers, especially those of Carriers. *Am. J. Hyg.* 15:809, 1932.
11. Faust, E. C.: Amoebiasis in the New Orleans Population as Revealed by Autopsy Examination of Accident Cases. *Am. J. Trop. Med.* 21:35, 1941.
12. Johnson, Carl M.: Observations on Natural Infections of *Endamoeba Histolytica* in Ateles and Rhesus monkeys. *Am. J. Trop. Med.* 21:49, 1941.
13. Mansohn-Bahr, P.: The Dysenteric Disorders, 1943, London.
14. Biggam, A. G., and Arafa, M. A.: The Sigmoidoscope as an aid in the Diagnosis of Dysenteric Conditions in Egypt. *Tran. Roy. Soc. Trop. Med. and Hyg.* 24:187, 1930.
15. Meleney, H. E.: The Pathology of Amoebiasis. *J. A. M. A.* 103:1217, 1943.
16. Reese, C. W.: Pathogenesis of Intestinal Amoebiasis in Kittens. *Arch. Path.* 7:1, 1929.
17. Spector, B. K.: The Pathological Changes Produced in the Intestines of Kittens by *Endamoeba Histolytica* with and without certain added Bacteria. *Am. J. Hyg.* 22:366, 1935.
18. Cleveland, L. R., and Sanders, E. P.: The Virulence of a Pure Line and several Strains of *Endamoeba Histolytica* for the Liver of Cats, and the relation of Bacteria. *Am. J. Hyg.* 12:169, 1930.
19. Hargreaves, W. H.: Chronic Amoebic Dysentery. *Lancet* 2:68, 1945.

Banti's Syndrome Following Prolonged Infectious Hepatitis

A REPORT OF TWO CASES

RALPH LEE FISHER, A.B., M.D., F.A.C.P.*†

and

MORRIS ZUKERMAN, A.B., M.D.*†

DETROIT, MICH.

BANTI'S syndrome has been defined as "a chronic disease of unknown origin, probably toxic, and primary in the spleen, and characterized by splenomegaly, anemia, and leukopenia, a tendency to gastric hemorrhage, increased formation and destruction of blood cells, and later by cirrhotic changes in the liver, with ascites and jaundice." (1).

In 1866, Griesinger and Gretzel employed the term "splenic anemia" for cases of anemia associated with chronic splenic enlargement; however, it remained for Guido Banti, in 1883, to give the first description of splenic anemia as a separate pathological entity. In 1894, 1898, 1910, he again described the symptom-complex which is now known as Banti's syndrome. At the time of his description, Banti divided the illness into three stages. Stage I, the pre-ascitic stage, (now ordinarily called splenic anemia), is characterized by an enlarged spleen, anemia, normal to low white blood count and normal to enlarged liver. He believed this stage lasted from 3 to 12 years. Stage II, intermediary stage, which generally persisted for a few months, is distinguished by gastrointestinal disturbances, occasional hematemesis, an increase in the anemia, an increase in the size of the liver, and a small amount of urine which contains bile pigments. Stage III, ascitic stage, is characterized by ascites, decrease in liver size, increase in the degree of anemia, and usually death within 6 months. Banti felt that in the third stage, the syndrome was indistinguishable from Laennec's cirrhosis. (2).

A definite etiology for Banti's syndrome has never been proven and many investigators feel that the syndrome may be caused by multiple etiological factors. Banti's original explanation of the etiology was that a toxic agent was brought to the spleen by way of its artery to act as a direct toxin, or possibly, to be converted into a "splenotoxin". (1). Thompson (3) stresses the fact that Banti's syndrome is the result of the mechanical obstruction to the flow of blood within the portal system. He maintains that the obstruction must be of such nature that a chronic increase of pressure in the splenic vein occurs. The venous pressure in the peripheral circulation should be approximately normal. He feels that the differences in heads of pressure is sufficient to cause splenomegaly.

The spleen in Banti's syndrome is usually large and firm, weighing from 800 to 900 grams. The capsule is thickened, having a beefy appearance when cut. Microscopically, there is a dilatation of the sinuses, with a fibrosis of the organ. Periarterial hemorrhages are

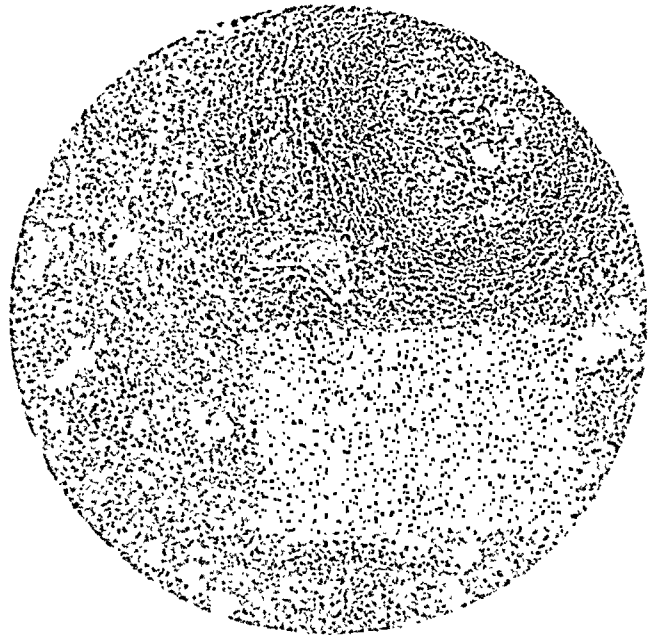


Fig. No. 1. This photomicrograph shows a typical area in a section removed from the spleen of Case No. 2. At the upper right is a malpighian corpuscle of normal size. A number of the corpuscles did show some ankyloid. The remainder of the photomicrograph shows red pulp with sinusoids which are dilated and engorged with red cells. There is a scattering of cuboidal cells lining the sinusoids. While the interstitial tissue is increased and fibrosed, this is but moderate. The trabeculae are not prominent nor are hemorrhages found around the central arteries.

Hematoxylin and eosin; X 125

also noted frequently. Siderotic nodules are often found and have been interpreted as an indicator of the portal blood pressure. Other pathological findings are degenerative changes in the splenic and portal veins. These lesions are commonly a phlebosclerosis, endophlebitis and atheromatous changes. The liver may or may not show a cirrhosis of the atrophic (Laennec) type. The bone marrow is mainly hyperplastic. (4).

From the clinical and laboratory standpoint, this condition is seldom difficult to diagnose. In the majority of the cases, the syndrome begins in the young, healthy individual of either sex and is characterized by an insidious onset. Digestive disturbances are frequent and great stress has been laid on early morning nausea and anorexia. The spleen, by definition, is always en-

*From the Department of Internal Medicine, Riverside Clinic, Detroit, Michigan.

†Formerly of the Department of Internal Medicine, Alexander Blain Hospital, Detroit, Michigan.

*Submitted June 1, 1946.

larged in this condition and classically is stated to be enlarged from stage I until termination of the disease or until removed.

Hematemesis or melena is often the initial complaint, the blood coming from a ruptured gastric or esophageal varix. These hemorrhages may be recurrent. Bleeding from the gums and epistaxis are very troublesome to control when they appear. Weakness and pallor are frequent early complaints. Jaundice has been described as classically appearing in the second stage of Banti's syndrome. Other skin changes consist of extensive purpura, ecchymoses and spider nevi, particularly of the face, shoulders and trunk.

In the late stage of this condition marked ascites is present as well as an increase in the icterus, and a palpable, nodular, contracted liver. In the initial phase of this syndrome there is liver enlargement. The patient ordinarily shows a moderate anemia which is frequently of the hypochromic type, although the macrocytic form has been described. The bone marrow shows evidence of hyperplasia. There is a low to normal total white blood count, with a decrease in the polymorphonuclear cells and a relative lymphocytosis. There is an accompanying thrombopenia. The X-ray examination sometimes confirms the diagnosis by revealing varices of the stomach and esophagus. The remainder of the laboratory work is non-specific insofar as facilitating a diagnosis. The icteric index is elevated. The urine is usually dark and contains excessive urobilin. The stools contain bile pigments and may or may not be altered in color. The cholesterol content of the blood is elevated. Liver function tests may be perfectly normal, or may show evidence of liver disease. The liver tests most frequently used are cephalin-flocculation, galactose tolerance, hippuric acid (oral and intravenous) and bromsulfalein tests.

The following conditions must be ruled out in making the diagnosis of Banti's syndrome: hemolytic icterus, syphilis involving the liver and spleen, Hodgkin's disease (especially the type in which the condition is localized early to the spleen and liver), Gaucher's disease, pernicious anemia, aleukemic leukemia, Hanot's cirrhosis, Laennec's cirrhosis when seen in the late stages, thrombosis or sclerosis of the portal and/or splenic veins, rare tumors of the spleen, such as a sarcoma or hemangio-endothelioma, and primary splenic neutropenia.

The treatment of Banti's syndrome may be divided into medical and surgical. Medical therapy has been advised where the patient is in too poor a condition to tolerate surgery or where surgery has failed to give a cure. The medical measures utilized have consisted of a high carbohydrate, high protein, low fat and high vitamin content diet. In addition to this choline chloride up to 6 grams a day is given. Usually such regime is employed where the condition is far advanced and liver cirrhosis exists. Mercurial diuretics plus ammonium

chloride are administered and abdominal paracentesis is carried out to eliminate ascites. Drenckhahn (5) has advocated venepuncture and the withdrawal of from 200 to 400 cc of blood to prevent hematemesis from a ruptured varix. The rationale in this therapy is to decrease the blood viscosity which in turn improves the circulation through the liver thereby reducing the burden on the collateral circulation. Small transfusions given slowly are employed where the anemia endangers the patient's life. Other procedures used are directed to specific causes of this syndrome such as the use of anthelmintic drugs for *Schistosoma mansoni* infestations. (6).

Surgical procedures advised are splenectomy when feasible and ligation of the splenic artery when the adhesions around the spleen are so dense that splenectomy is contraindicated. Other procedures are Talma's operation (omentopexy), injection of the esophageal varices and ligation and injection of the coronary and other veins around the upper end of the stomach to prevent hematemesis. Babcock (7) has suggested peritoneosaphenous or peritoneofemoral vein anastomosis to care for the ascites in the late stage of the condition.

The prognosis in Banti's syndrome is variable. Spontaneous recovery does not occur. The results expected from splenectomy depend on the extent of the preceding liver damage, being worse with extensive involvement of the latter organ. Eliason and Stevens (8) feel that splenic surgery should be carried out as early as possible and have reported patients who have lived 20 years after this procedure. Cecil (1) states that Whipple noted improvement in two-thirds of his cases who were subjected to this operation. Howells (2) reported 51 cases, representing the three stages of Banti's syndrome treated by splenectomy and has definitely felt that this operative procedure did not improve the life expectancy.

Death in Banti's syndrome usually results from intercurrent infections, such as pneumonia, peritonitis, cholemia, massive hemorrhage from esophageal or gastric varices and surgical intervention.

Case 1. Miss H. H. a 19 year old white female, was first seen in the clinic on October 12, 1931. At that time she was treated for scabies with complete cessation of symptoms. One year later she was again examined and was treated for bronchial asthma, chronic flexural eczema and furunculosis of the buttocks. Improvement was noted under conservative therapy. The patient was next seen on September 26, 1938 for treatment of a sebaceous cyst of the right cheek.

On December 7, 1943, the patient presented herself in the Out Patient Department. She stated she had been in good health until one year previously when she began to experience marked fatigue, drowsiness and sluggishness, "as though she could sleep all day and night". During July, 1943 she developed anorexia, nausea and generalized weakness. In the middle of

September, 1943 she noticed a yellow discoloration of the skin, associated with a marked itching sensation. She also observed the "whites of her eyes were yellow". She complained of a bitter taste in her mouth for one day. Since the onset of her illness she had noticed that her urine was dark in color. She had gained one pound during the past month. There was no history of abdominal pain, previous transfusions, injections of serums, bleeding readily after being cut, diarrhea, consistent use of drugs, swelling of the feet, contamination of food in any manner or hematemesis. The past history was noncontributory.

Physical Examination: The patient was a well developed, well nourished young girl, not acutely ill. There was mild generalized icterus with excoriated areas of the skin. The sclerae showed a definite icteric tint. The fundi, nose and throat were negative. The breasts were normal, there was no generalized lymphadenopathy and the lungs were clear to percussion and auscultation. The heart was not enlarged to percussion and no murmurs were heard. Examination of the abdomen revealed an enlarged liver, palpable one fingerbreadth below the costal margin, but was not tender. The spleen was not definitely palpable. The neurological examination was negative, the extremities showed no edema and the spine was normal. X-ray examination of the chest was essentially negative except for bilateral cervical ribs. The oral cholecystography revealed a poorly visualizing gall bladder.

Laboratory Studies: The hemoglobin was 91% (14 grams) with a red blood count of 4,640,000 and a white blood count of 4,200; the color index was 0.98. The differential count showed 35% lymphocytes, 63% polymorphonuclear cells with 62% filamented and 1% non-filamented and 2% eosinophiles. The Kline test was negative and the icterus index was 30 units. The urine showed the following: specific gravity was 1.025, acid reaction, sugar and albumin were negative, urobilin and urobilinogen 4 plus and bilirubin 2 plus. The Van den Bergh test showed a very faint, delayed reaction. Following the galactose tolerance test 2 grams were excreted in the urine and after the oral hippuric acid test 1.8 grams were recovered in the urine. Gall bladder drainage done January 8, 1944 revealed large clumps of white cells, no crystals were found but large amounts of mucus and epithelial cells were present.

A diagnosis was made of infectious hepatitis with suspicious early Banti's syndrome and the patient was put on a high carbohydrate, high protein and high vitamin diet. Gall bladder drainages were done at two week intervals which tended to decrease the pruritus. The patient was examined in the Out Patient Department at one to two week intervals but failed to improve materially. Follow-up examinations indicated that the liver was becoming larger and on March 11, 1944 the liver was enlarged three fingerbreadths below the costal margins. One month later laboratory studies re-

vealed an icterus index of 16.6 units and the Van den Bergh test showed a direct, immediate reaction. The prothrombin time was 15 seconds and the bromsulfalein test (in the presence of icterus) revealed 35% of the dye retained in 30 minutes and 30% retained in 60 minutes. The red blood cell fragility test showed hemolysis began in 0.38% saline and was complete in 0.26%. Agglutination tests against leptospira icterohemorrhagiae and leptospira canicola were negative; the Rh factor was negative.

In July of 1944 the patient began to complain of frequent epistaxis and it was noted that she was gaining weight. On July 27, 1944 the patient was hospitalized. Early in the morning of the day of admission she began to have a profuse nasal hemorrhage which was constant except for a short time when the bleeding was controlled by packing the nose with cotton. At about 3 P. M. she had an emesis of dark brown blood.

At the time of this admission the patient weighed 150 pounds. She was not acutely ill, but had a moderate icteric tint to the skin with multiple areas of excoriation. The sclerae were also moderately icteric. There was fresh blood in the posterior pharynx. On examination of the abdomen, the spleen and liver were not enlarged on palpation or percussion. Hemoglobin at this time was 54% with a red blood count of 2,730,000, a white blood count of 4,800 and a color index of 1.00. The differential count showed 50% lymphocytes, filamented neutrophils 41%, nonfilamented 2%, eosinophiles 6% and basophiles 1%. The red blood cells showed marked anisocytosis and slight poikilocytosis. There were no features of the blood smears suggestive of familial hemolytic icterus. The icteric index was 29 units and the prothrombin time was 22 seconds. The bleeding time was 3¼ minutes and the coagulation time was 5½ minutes. The specific gravity of the urine was 1.020; it was acid in reaction, sugar and albumin were negative and bile and urobilinogen were 3 plus.

During the period of hospitalization, a total of 3250 cc of whole blood was administered and upon discharge from the hospital on August 9, 1944, the hemoglobin was 81% with a red blood count of 4,020,000.

When the patient was again seen three days later, abdominal examination revealed a palpable spleen. A tentative diagnosis of Banti's syndrome was made and a splenectomy was recommended. Permission to perform the operation was refused.

The patient was then referred to another clinic for consultation on August 15, 1944 and was given thorough diagnostic studies. The report sent to us after all the necessary examinations were completed revealed the following positive points: slight jaundice of the sclerae and a palpable spleen. The hemoglobin was 82% (12.7 grams) with a red blood count of 4,600,000 and a white blood count of 3,150. The differential count revealed 47% neutrophils, 22% small lymphocytes, 14% large lymphocytes, 4% eosinophiles

and 13% monocytes. The hematocrit was 39.6 and the mean corpuscular volume was 98 cubic microns; reticulocytes numbered 2.5%; the red blood cells appeared to be well colored and there was slight anisocytosis and poikilocytosis. There was a definite diminution in the number of platelets and the sedimentation rate was 35 mm per hour, which was increased 10 to 15 mm according to the method used. Serum bilirubin was 1.45 mg. and the serum albumin was 2.9%. There was a hypoglycemia, the fasting blood sugar being 57 mg.% with a fall to 35 mg.% at the end of three hours.

The sternal marrow showed a picture which was interpreted as normal, there being no evidence of leukemia, malignant infiltration or maturation abnormality.

The liver function tests showed the cephalin flocculation test to be positive and the bromsulfalein test showed 70% retention. It was felt that the reliability of the bromsulfalein test should be questioned because of the slight jaundice. It was also felt that the blood which was examined was made up in a large part of the red cells supplied by the donors as a result of her recent transfusions.

X-ray examinations revealed a negative upper gastrointestinal tract. There was an indentation along the greater curvature of the stomach which was thought to be due to the enlarged spleen. Cholecystographic films were indefinite. There was a horizontal shadow close to the liver margin which could not be identified, under exposure and improper position might have accounted for this. No definite diagnosis was returned by the consultant, but his impression was that of biliary or hypertrophic cirrhosis.

The patient was not seen by us until May 17, 1945, at which time she was hospitalized. She complained of being very tired and sleepy for two weeks with joint pains for one and a half weeks. She stated she had been following the high carbohydrate, high protein and high vitamin diet up to the time she entered the hospital. Two weeks previous to admission she developed an upper respiratory infection which gave her a marked rise of temperature, although she did not know the highest degree of temperature rise. Since that time she had felt very drowsy and fatigued. About a week and a half before admission she began to note a swelling of her ankles and lower extremities and began to have a severe pain in her right elbow, followed by pain in the right knee, then the left knee and finally both ankles. The involved joints were never red. She continued to complain of bleeding from her gums.

The temperature at the time of physical examination was 99 degrees and her weight was 145 pounds. The patient was obese and appeared very lethargic. The skin was icteric and muddy, with multiple excoriated areas and there was marked oozing from the gums, but no associated hyperplasia. There was icterus of the sclerae. The heart was not enlarged to percussion, P_2

was accentuated and there was a soft systolic murmur heard at the apex. Examination revealed a distended abdomen with the liver palpable five fingerbreadths below the costal margins with hard nodules of the left lobe. The spleen was also enlarged five fingerbreadths below the costal margins. No definite fluid wave or percussion dullness in the flanks could be detected. Rectal examination revealed small external hemorrhoids. There was slight edema of the legs with marked pain of the knees on motion.

The hemoglobin at this time was 46% with a red blood count of 2,280,000, white blood count of 2,950, color index of 1.04 and a platelet count of 61,000. The differential count revealed 57% filamented neutrophils, 5% non-filamented and 38% lymphocytes. The blood urica was 17.1 mg.%. The specific gravity of the urine was 1.010; the reaction was alkaline and the sugar and albumin were negative. The electrocardiogram was interpreted as left axis deviation.

The following diagnoses were made: Banti's syndrome with Laennec's cirrhosis, secondary anemia, rheumatic fever and obesity. The course in the hospital was very stormy. The patient was in a state of cholemia, had continual bleeding from the gums and there was intermittent elevation of the temperature varying from 98.6 to 103.6. The patient refused to eat. Small transfusions of Rh negative blood were given. At this point it was felt that the patient's condition would not tolerate surgery. The patient then insisted upon continuing her treatment at home and was discharged May 26, 1945.

We did not hear from the patient until November of 1945 when she notified us that her abdomen was becoming markedly distended and that she was having difficulty in breathing. She was also complaining of tarry stools. Thirteen quarts of ascitic fluid were removed by another physician. Since this last communication, she had entered another hospital where she had been given large numbers of transfusions, amigen solution intravenously and plasma. Because of a right hydrothorax which impaired her breathing, thoracentesis was performed twice. The patient's weight had fallen from 165 to 124 pounds and her icterus index was down to 12 units. At the time of writing this article, the platelet count is 121,000, hemoglobin 10.2 grams and the prothrombin time 52 per cent. The patient continues to bleed from the gums.

Case 2. Mrs. C. W., age 50, was first seen in the Out Patient Department on April 23, 1945, stating she had been in good health until one year previously. In the past year she had lost considerable weight, 45 pounds, and was prone to fatigue easily. This had been accompanied by marked anorexia. Her menses ceased seven months previously and at the time she was first seen she was experiencing many hot flashes. During the past two weeks the patient had become conscious of the "whites" of her eyes becoming yellow.

She also felt that she had "gas on the stomach", especially if she ate fried or greasy foods. She denied post-prandial pain located in the epigastrium which might be relieved by food or alkali. She also complained of constipation of two weeks duration. There was no history of severe right upper quadrant pain, contamination of food such as by rats, mice or roaches, transfusions, injections of medication, consistent use of drugs, diarrhea, bleeding readily from minor lacerations, swelling of feet, vomiting of blood (dark or bright red), passing of tarry stools or of alcoholism. The past history was noncontributory.

The patient was a middle aged women, 5' 4 $\frac{1}{4}$ " tall, weighing 165 pounds. The temperature and pulse were normal. She appeared subacutely ill. The skin was moderately icteric as were the sclerae. There was tenderness in the epigastrium on palpation, the left lobe of the liver was enlarged but not nodular. The spleen was not palpable. There were dilated, tortuous veins of both legs.

Laboratory Studies: The hemoglobin was 78% with a red blood count of 4,000,000 and a white blood count of 9,200; color index was 0.98. The differential count showed 73% neutrophils, 25% lymphocytes and 2% eosinophiles. The Kline test was negative. The red blood cell fragility test revealed hemolysis beginning at 0.42% and complete at 0.28%. The icterus index was 16 units. The urinalysis was normal. The galactose tolerance test gave no return of galactose in the urine and the hippuric acid test gave a value of 3.5 grams. The Ewald test meal revealed 4 degrees of free hydrochloric acid, 2.4 degrees of combined acid and 6.4 degrees of total acid. The stool examined for occult blood was negative. The basal metabolic rate was plus 11%.

X-ray examinations revealed an essentially normal chest, poorly functioning gall bladder, diverticulosis of the colon and a normal upper gastro-intestinal tract. The diagnoses made were as follows: Infectious hepatitis, obesity, menopausal syndrome, diverticulosis of the colon, bilateral varicose veins and chronic constipation.

The patient was put on a regime consisting of a high carbohydrate, high protein, low fat and high vitamin diet and choline chloride drachms 2, after meals. Brewer's yeast was given to fortify the diet. Gall bladder drainages were done weekly and 1 cc liver was given intramuscularly at each office visit. The patient was seen at frequent intervals but showed very little improvement. On October 5, 1945 the icterus index was 60 units. Approximately one month later a definite palpable spleen was found and the diagnosis of Banti's syndrome was considered. The patient was hospitalized on November 14, 1945 for further study.

On admission the patient's temperature was 99.2. She appeared subacutely ill, was very icteric and there was marked icterus of the sclerae. Examination of the abdomen revealed a firm, smooth liver, palpable five

fingerbreadths below the costal margins and the spleen palpable three fingerbreadths below the costal margins. The hemoglobin was 74% with a red blood count of 3,710,000 and a white blood count of 6,150. The color index was 1.0. The differential count revealed 74% filamented neutrophils and 4% non-filamented, 18% lymphocytes, 3% eosinophiles and 1% basophiles. The bleeding time was 50 seconds and the coagulation time 3.5 minutes. The urinalysis was negative for sugar and albumin, revealed bile 1 plus, bilirubin 4 plus, urobilin 3 plus and a trace of urobilinogen. There was 65% of the dye retained in the bromsulfalain test (patient icteric). The prothrombin time was 10 seconds. The icterus index was 67 units. The Van den Bergh test gave a positive, prompt, direct reaction and the galactose tolerance test was negative. The serum albumin was 3.5 grams and the serum globulin 2.1 grams, giving a total protein of 5.6 grams. The albumin-globulin ratio was 1.7 to 1. The hippuric acid test revealed 3.1 grams excreted and the stool gave a 4 plus urobilinogen reaction.

Two weeks after admission the patient's hemoglobin was 61% (9.5 grams) with a red blood count of 2,850,000 and a white blood count of 7,850. The color index was 1.07. The differential count revealed 66% filamented neutrophils and 7% non-filamented, 19% lymphocytes, 6% eosinophiles, 2% basophiles. The urinalysis was essentially negative.

The diagnoses made at that time were Banti's syndrome, secondary anemia and obesity. On November 29, 1945 a splenectomy was performed. The spleen was very large but the liver was not grossly cirrhotic. The post-operative course was complicated by a left side pleural effusion and a wound infection. On December 5, 1945 the white blood count was 22,150 indicating that the patient could respond to infection. Four days later 1400 cc of straw colored fluid were removed from the left chest.

The pathological report on the spleen removed at operation described the organ as measuring 12.5 x 8.5 x 21 cm. and weighing 800 gms. The surface was roughened. On cut section, the Malpighian bodies were prominent. The microscopic diagnosis was splenomegaly, consistent with chronic passive congestion of the portal circulation which could be associated with cirrhosis of the liver or thrombosis of the portal vein.

The icterus index on December 5th was 75 units and on December 18th, 50 units. The patient was discharged from the hospital on December 21, 1945. The patient was last examined on January 6, 1946, at which time it was observed that she was less icteric and reportedly felt stronger. There was a small pleural effusion on the left and the liver was palpable 3 fingerbreadths below the costal margins. It was also noted that the operative wound was still draining a small amount of purulent material.

Discussion: Two cases have been presented which we

feel began as infectious hepatitis, developed a prolonged clinical course with very little improvement on a medical regime, and were eventually characterized by the classical signs of Banti's syndrome.

The etiology of Banti's syndrome has never been established beyond doubt. The two main theories considered at the present are a portal hypertension and a toxic factor. Factors tending to make for portal hypertension are *Schistosoma mansoni* infection, cirrhosis of the liver, ptosis of the spleen and portal or splenic vein thrombosis. No toxic factor has as yet been isolated or found capable of reproducing this condition. Dietrich (9) has called attention to the fact that catarrhal icterus and epidemic hepatitis are probably identical diseases of virus origin and they may lead to cirrhosis of the liver.

A brief analysis readily shows the reasons for considering our cases as infectious hepatitis early in the clinical course. Acute infectious hepatitis without jaundice has become a recognized clinical entity. Owing to obvious diagnostic difficulties, this condition will often go unrecognized and the treatment is inadequate; consequently, the liver pathology progresses and jaundice supervenes or the subicteric stage persists for many months without any improvement. This condition has been as common as the acute hepatitis with icterus. The onset of acute infectious hepatitis without jaundice is characterized by an enlarged liver, anorexia, nausea and vomiting, vague gastro-intestinal symptoms with ill defined abdominal discomfort, gaseous eructation, easy fatigability and lassitude. Exercise tolerance tests have revealed some interesting factors in regard to this hepatitis. If the activity of the hepatitis is present, exercise will have a tendency to increase all of the manifestations of the condition as physical findings, symptoms and laboratory evidence. Exercise in the subicteric stage of acute infectious hepatitis may cause a definite relapse which will run a more severe and prolonged attack than did the initial attack. (10) We feel that the preceding year's illness of our patients before entering the hospital may be interpreted as an acute infectious hepatitis without icterus, but which was kept from clearing by the patient's continued activity and improper medical care.

Icterus appeared in both of our cases before splenic enlargement could be detected either by X-ray or physical means. This is the reverse of that seen in Banti's syndrome. Anemia was not present in the cases presented at the time that the icterus was first

detected; again this is the opposite of that seen in the usual clinical description of Banti's syndrome. Case 2 presented a greater degree of icterus after a 5½ month interval than does the ordinary case of Banti's syndrome. In addition, both of these cases were seen at the time when infectious hepatitis was a frequent occurrence. The history and laboratory examinations (also operative findings of Case 2) did not reveal any other causes of the icterus.

CONCLUSIONS

- I. Two cases of infectious hepatitis leading to Banti's syndrome have been presented, together with a review of the literature.
- II. Factors present in these cases which necessitated the diagnosis of infectious hepatitis when first seen, and after careful clinical observation were:
 - A. There were present prolonged prodromal symptoms of one year's duration in each case, which were interpreted as infectious jaundice without icterus.
 - B. Jaundice appeared before splenic enlargement (either by X-ray or physical signs) which is the reverse of the ordinary case.
 - C. Jaundice in Case 2 was more pronounced than in the usual case of Banti's syndrome.
 - D. Patients with Banti's syndrome usually present an anemia at the time of jaundice, but this did not occur in our cases.
 - E. The cases reviewed presented themselves for treatment at the time that many cases of infectious hepatitis were being diagnosed.
 - F. The history and laboratory data (also operative report in Case 2) did not reveal any other cause for the clinical picture.

III. All cases of infectious hepatitis that clear up slowly should be followed very carefully; if the spleen becomes enlarged, or larger, splenectomy should be done, if not contraindicated. Early splenectomy, at the optimal time has been stated to prevent liver cirrhosis.

IV. All other causes of jaundice should be ruled out before making a diagnosis of infectious hepatitis with a prolonged clinical course. This is especially true of carcinoma of the pancreas or biliary tract.

V. If infectious hepatitis is a related factor in the etiology of this condition, then a virus or toxic etiological agent must be proposed as one of the many causative agents in the production of Banti's syndrome.

REFERENCES

1. Cecil, Russell L. A Textbook of Medicine. W. B. Saunders Co., Philadelphia, 5th Edition, 1940, pp. 1389-1391.
2. Howells, L. Treatment of Splenic Anemia and Banti's Syndrome. *Lancet*, 1938, 1:1320-1324, June 11.
3. Thompson, William P. The Pathogenesis of Banti's Disease. *Ann. Int. Med.*, 1940, 14:255-262, Aug.
4. Boyd, William. A Textbook of Pathology. Lea and Febiger, Philadelphia, 3d Edition, 1939, pp. 820-822.
5. Drœckhahn, C. H. A new Approach to the Prevention of Hemorrhages from Esophageal Varices as Occur in Cirrhosis and Banti's Disease. *A. M. J. Digest, Dis.*, 1939, 6:462-465, Sept.
6. Almy, Thomas P. and Harper, J. G. Mason. Banti's Syndrome Apparently Due to Infection with *Schistosoma mansoni*. *J. A. M. A.*, 1944, 126:703-705, Nov. 11.
7. Babcock, Wayne W. Principles and Practice of Surgery. Lea and Febiger, Philadelphia, 1944, p. 915.
8. Eliason, E. L. and Stevens, L. W. Surgery of the Spleen in Blood Dyscrasias. *Surgery*, 1943, 13:177-187, Feb.
9. Dietrich (Deutsche Med. Wchnschr. 68:1, Jan. 2, 1942) Quoted from Epidemic Jaundice, J. A. M. A., 1943, 123:1066, Dec. 18.
10. Barker, M. Herbert, et al. Acute Infectious Hepatitis in the Mediterranean Theater. *J. A. M. A.*, 1945, 128:997-1003, Aug. 4.

The Pathogenesis and Mechanism of Cirrhosis of the Liver

By

ABRAHAM O. WILENSKY, M. D.

NEW YORK, N. Y.

THERE is a good deal of looseness in the usage of the term cirrhosis. In this communication, the term cirrhosis, when otherwise not modified, is synonymous with the terms atrophic cirrhosis, portal cirrhosis, and/or Laennec's cirrhosis, as ordinarily employed. It indicates a chronic progressive fibrosis of the supporting interlobular stroma of the liver, i.e., a chronic interstitial hepatitis. It is characterized, anatomically, by the restriction of the essential lesion to an extralobular distribution and by its interlobular location in the connective tissue septa of the liver. It does not include any form of pyogenic, tuberculous, luetic, or other similar form of pathology, which because of their known causal agents, are so automatically differentiated in separate groups. The term alcoholic cirrhosis is mentioned only to be condemned because it indicates a causal relationship which is not satisfactorily established. Hypertrophic cirrhosis of the liver (Hanot type) is an entirely different disease and is not discussed here.

Up to very recently, the viewpoints and assumptions, which have been held, or made as regards any and all phases of the problem of the pathogenetic origin and mechanism of chronic progressive fibrosis, or cirrhosis, have not been securely based. True knowledge of the normal structure and architecture of the liver and of the pathological changes which occur in hepatic disease have been studied and were fairly accurately known for many years. Nevertheless, the conclusions based on the latter could most often only be conjectures, because the facts obtained were concerned with long standing disease, and there was little or no observations of the early stages of the latter. Even the early laboratory work was done, therefore, at the wrong time, was almost always insufficient, and often not done at all. While these deficiencies have been remedied to a very large degree by the greatly increased facilities which have been provided and by the increased and more productive research activity of the growing numbers of investigators, this has applied only to acute disease of the liver, so that the problem of chronic progressive fibrosis or cirrhosis has not benefitted materially thereby.

The factual knowledge involved upon which an understanding of the essential nature of hepatic cirrhosis must be based, and their proper integration, must include a study of the structural components and the general architecture of the liver, and a study of the various lesions of the latter individual elements. Lesions

of the parenchymal structure are especially important because it is possible to study them at their inception, or at very early periods of their development, and to follow the recovered cases for relatively long periods thereafter, in order to determine whether cirrhotic conditions follow either as a consequence, or for some other associated or unassociated reason. This has only been done in the last few years.

The structural components of the liver include (1) the parenchymal cells; (2) the supporting framework including the reticulo-endothelial system; (3) the vascular channels including the sinusoids; (4) the lymphatic channels; and (5) the excretory duct system. The neurological mechanism is not included in this discussion because, to my knowledge, there is no observed or described disease of the latter.

THE ARCHITECTURE OF THE LIVER

From a clinical as well as an anatomical standpoint, the general architecture of the liver consists essentially of a frame-work in which the parenchymal cells are nested with great physical ingenuity so that a maximum of secreting surface is provided in a minimum of space. The framework, in relation to the entire organ, is relatively and actually at a minimum, is maintained in its normal distended position by the hepatic parenchymal cells, which it contains, and is anchored by the mass of the latter and by its attachment to the capsule of the liver. The framework is freely distensible, so that the mass of the organ under various physical conditions—hyperemia, etc.,—becomes larger. Contrariwise, when destructive parenchymal lesions occur, shrinkage of the organ follows and is easily perceived clinically. The framework makes up the normal stroma of the liver. It consists of mesoblastic connective tissue which is only apparent as the stroma in the interlobular septa and in Glisson's capsule where it surrounds and supports the triad of hepatic artery, hepatic vein and bile duct radicals.

Penetrating into the lobules, there is a derivative of the interlobular stroma, the reticulo-endothelial systemic network, which is of equal importance physiologically to any structural supportive function which it may have been anatomically. The reticulo-endothelial system forms the walls of the sinusoids and its fibrils extend between the individual cells of the liver cords; it contains also the large Kupfer cells.

In the form of pathology in which destruction of the liver parenchymal cells is complete, this connective

tissue and reticulo-endothelial framework remains and can be visualized in microscopic anatomical studies.

THE BLOOD SUPPLY OF THE LIVER

The blood supply of the organ is derived from two sources, which apparently are independent of each other both structurally and functionally:

1. The portal vein gathers the blood from the entire digestive and absorbing part of the intestine, and in its final anatomical analysis passes the collected blood through the parenchymal system of the liver to empty into the hepatic vein and inferior vena cava.

The portal vein also picks up the entire return blood supply of the spleen and pancreas.

2. The hepatic artery has no relation to the portal venous efferent network and comes directly from the coeliac axis without relation to the gastro-intestinal tract or its vascular supply.

The important functional fact to remember is that interruption of the arterial current in the hepatic artery, both experimentally and in operative accidental division, regularly produces necrosis of the liver,—the entire liver if the main trunk is involved or the appropriate lobe if the major right and left hepatic branches are involved. Interruption of the portal stream does not have this effect. In the exceptional case, in which hepatic necrosis follows the latter conditions, it must be assumed that there has been simultaneous interruption, either partial or complete of the hepatic artery blood stream.

The venous return of the hepatic artery, while independent of the portal network, nevertheless also empties finally into the hepatic veins outside of the confines of the liver lobule.

PARENCHYMATOUS CELLULAR DISEASE

Disease of the parenchymal cells of the liver is either an acute destruction and necrosis of the cells, or a chronic, long continued degenerative process leading to changes in the intimate structure of the cell.

ACUTE PARENCHYMATOUS DISEASE

Acute parenchymatous disease of the liver, or, as it is commonly called, acute hepatitis, occurs under a variety of conditions, usually differentiated because of geographical distribution, because of assumed various causation, as well as because of intensity of manifestations. The term includes, (1) acute hepatitis; (2) epidemic hepatitis; (3) catarrhal jaundice; (4) epidemic jaundice; (5) yellow atrophy; (6) infective or infectious hepatitis, including the English (11), German (27), Scandinavian (26), Middle Eastern (17), Egyptian (15), (24), etc., types, and (7) the American type (22), (2), including homologous serum jaundice (23). In all of these, the essential pathological process is similar.

Acute parenchymatous disease occurs in all degrees

of severity from very mild, subclinical, latent, frequently unrecognized disease, to the most virulent, hyperacute necrosis of the liver cells of a wide area of, or the complete liver. In the latter, it occurs in epidemic form as well as sporadically; and, in military environments, it has been and is now a frequent and common disabling factor. Acute and hyperacute forms of yellow atrophy of the liver and the epidemic forms of acute hepatitis occurring in the army are the outstanding examples of this form of disease.

In acute parenchymatous disease, the lesion is limited entirely to the parenchymal cells (Lucké (20), Turner, Snavely, Grossman, Buchanan and Foster (30), Cockayne (6), Dietrich (7), Klemperer, Kilian and Heyd (16), Gaskell (12), Barker, Capps and Allen (1), etc., etc.). The other structures are not involved: the connective tissue stroma, including the reticulo-endothelial system, and the contained vascular, duct, and neurological channels are lesion free. There is, however, in these acute cases, much evidence of lymphatic involvement and transmission in the presence of swollen glands in the appropriate lymph node chains.

When recovery takes place, the parenchymal cells regenerate from the few cells which had not been previously destroyed and/or from the bile canaliculi and fill up their former position in the uninjured framework. In about half of the recovered cases, the return to normal is complete, anatomically, functionally and symptomatically. In the remainder, there are continued evidences of parenchymal disease,—a rather indistinct, vague and frequently unrecognizable symptomatology, demonstrable changes in liver function, variable bouts of jaundice—either continuously, or with remissions, recrudescences and/or exacerbations. Since the time when clinical and laboratory observations have been reliable, there is not sufficient evidence to say conclusively that connective tissue changes have or will eventually follow as a consequence of the epidemic form of disease. However, there are a few reports of such eventualities from the sporadic forms of the disease in civil practise, which indicate that this could and has happened (Polack (25), Caravati (5), Findlay, Martin and Mitchell (9), Wilensky (32), etc.). According to Lucké (20), this sequence has also been rarely observed after the epidemic form of the acute disease: but he considers this sequence only a coincidence and without causal relation.

CHRONIC PARENCHYMATOUS DISEASE

Chronic forms of liver parenchymal disease are fatty, albuminous, hyaline, and/or other degenerations within the cell structure. They result from long continued irritations and injuries of the cell which are commonly of a chemical and/or bacterial origin. The agents which are thought to cause such injuries include deficiencies in diet, especially of vitamin B; poisonous drugs (ether, chloroform, carbon tetra-

chloride, etc.); chemicals (phosphorous, manganese, copper, silica, coal tar, etc.), condiments and spices; various food poisons, and various products of metabolism. Alcohol especially has been incriminated.

Clinically, each hepatic parenchymal injury is found in certain physiological states, the most important of which is pregnancy, and in certain diseased conditions, the most important of which is thyrotoxicosis. Bacterial infection also is a most powerful parenchymal destructive agent and a frequent offender. And always it seems that some degree of inanition is present. All of these function by interfering with the nutrition of the liver cell, and in this interference it seems that anoxia is a most important factor.

Of all of these assumed causes, the only ones which can be more or less definitely incriminated, at least from a laboratory standpoint, are the chemicals, especially, the heavy metals and carbon tetrachloride. The latter has frequently been used for experimental production of hepatic disease. Alcohol has for many years been accepted, because of popular belief, as the most important causal agent and this belief has been increasingly accepted in medical circles also. However, this assumption has lately been questioned. It now appears either that alcohol functions as an important auxiliary to some other causal agent, or that the harm is due to chemicals incident to the manufacture of alcoholic beverages or to their storage in charred barrels. It also seems that other agents or conditions may, in addition to the alcohol, be cooperatively essential for the process to develop and among these infections and, certainly, various marked grades of inanition seem important.

It seems that bacteriologic infection may be an auxiliary to any of the other agents which can produce injury to the liver. Either the previous injury lessens the resisting power of the liver and so facilitates infection, or infection inhibits certain protective powers of the liver so that injurious substances are not destroyed or sufficiently neutralized before hepatic injury can be produced, or, if the latter is already present, infection facilitates its further progression.

Allergic sensitization plays an important role in the repetitive character of the process.

The differences in duration, in the manner of the development of this clinical and pathological complex, and the patency or latency of the clinical manifestations seem to have important relations to the size of the dose of the causative agent, to the number and frequency of its repetitions, to the time limit in which it is delivered, and to various forms of preceding sensitization of the body to diverse toxic bodies.

It is very difficult to establish the recognizable point at which any of these anatomical changes—i. e., cellular degenerations—reaches the plane of clinical observation. The problem of cellular change, which varies from purely functional abnormality to various grades of

cellular degeneration and destruction, must be considered as distinct from actual inflammatory change. And in the field of cellular functional or morphological change, one must note the lack of evidence of any hyperfunctional or hypertrophic change, or the evidence, difficult to demonstrate during life, of diminution in function and destructive change in cellular morphology, and one must note the enormous capacity of the liver for compensatory effort and regeneration.

Practically speaking, in most cases hepatic function is demonstrably maintained by compensatory effort; bile is still present in the stool; there is no impairment in glycogenesis; there is no evidence of failure to deamidize the amino-acids; urea formation is unhampered, and a progressive increase of nitrogenous products in the blood is not observed. In the latent cases, there is never present the clinical picture of a well-established disease, marked by abdominal distension, vomiting, rise in temperature, oliguresis, appearance of albumin, casts and red cells in the urine, increase of residual nitrogen in the blood, bleeding into the mucous surfaces, blood in the vomitus and the stool, and ascites or enlargement of the spleen. And there is never the opportunity for any detailed or sufficient study.

CHRONIC INTERSTITIAL HEPATITIS— CIRRHOSIS

There is never any distinguishable acute onset in hepatic cirrhosis. During the clinically observable course of the disease, episodes occur which might be termed acute; and, when, under such conditions, and in a previously unobserved case, it is thought that the illness is being ushered in by an inceptive acute phase, the latter should be interpreted as an intercurrent acute manifestation and/or exacerbation during the course of a chronic disease.

As ordinarily seen, chronic interstitial hepatitis, i. e., cirrhosis, is a chronic disease,—a chronic progressive hypertrophic fibrosis of the interlobular septal stroma of the liver. It is always associated with a variable form of chronic cellular degeneration of the liver parenchyma and with a state of general inanition. All of the causes which had been previously summarized in this communication as causal agents for the production of chronic parenchymatous cellular disease have, *ipso facto*, been assumed to be the provocative agents for the cirrhotic condition, on the theory that the cirrhosis results from the cellular degeneration, but this seems to be erroneous. There is experimental proof that more than one agent or condition may, and usually does cooperate in finally bringing about the cirrhosis; but this is, for the most part, a laboratory finding. And if we exclude the alcoholic cases, or those of out-and-out toxin and/or poison (e.g., heavy metals) produced cellular degeneration, and/or atrophic destruction with a possible associated and/or consequent interstitial fibrosis, there is little or any recognizable counterpart

of the mechanism of these laboratory phenomena in clinical medicine.

The anatomical changes which have been observed, are conveniently separated into stages: (1) the state of progressive interlobular connective tissue hypertrophy and fibrosis; and (2) the final stage of contraction of this scar tissue with resultant mechanical effects on the liver lobule and on the triads in the interlobular septa.

At whatever stage these cases come to anatomical examination, one finds either cellular degenerative change alone or, in addition, more or less atrophic cellular destruction beginning at the periphery of the lobule and progressing towards its center.

If one is perfectly candid, it is difficult to decide whether the cellular degeneration, or the interstitial fibrosis antedates the other. It is easy to say that the latter results as a consequence of the cellular degeneration. But it is just as easy to assume that the cellular degeneration is a consequence of the advanced inanition, which is always present, or that it is caused by the constructive action of the contracting scar tissue in the fibrotic interlobular stroma. Certainly, if the former were true, there should be present much more advanced cellular change as well as intralobular connective tissue change, but these changes are not present.

While there are undoubtedly variable symptomatologies during the first stages, it is true that the bulk of the observable subjective symptoms and demonstrable objective findings and manifestations occur in the last stage—the state of contraction of the fibrosis. This produces (1) pressure atrophic changes in the parenchymal cells of the lobules with consequent intensification of any functional changes which had previously existed; and (2) constrictive changes upon the vascular, duct and other channels contained in the interlobular stroma, including ascites and jaundice. Both of the latter are late phenomena in this disease. Modern knowledge has even changed these viewpoints, so that it is now believed that they are perhaps equally, if not entirely due to diminished cellular function, which leads to advanced stages of hypoproteinemia as a result of the inanition.

There is little evidence of any inflammatory reaction in such livers. Nevertheless, in the earliest stages observed the liver is enlarged, indicating some inflammatory process. There are no lymphatic enlargements in the appropriate lymph node chain either of an acute or of a chronic nature. This is to be expected. Any such reaction would be present during the inception of the disease, at the time when cases of cirrhosis never come under clinical, laboratory, or post mortem observation. Any possible acute episode during the clinically observed course of the illness, similarly yields no competent data. Furthermore, at the time cases of cirrhosis come to post mortem examination, any evidence of a previous acute, or subacute hepatic lymphangitis is lost in the interstitial fibrotic hypertrophy.

Splenic enlargement occurs late in the course of the disease and is commonly of minimum extent. All the evidence makes it safe to assume, that it is a secondary manifestation of the liver cirrhosis, that the mechanism of its enlargement does not include the pathogenetic mechanism of the liver cirrhosis, and that it undoubtedly is a mechanical effect due to obstructive interference in the portal vascular flow.

There are no recognizable changes in the reticulo-endothelial system especially of the part which lies within the confines of the liver lobule; nor is there any recognizable change in that part of the system which lies without the liver, especially in the spleen. Apparently in hepatic cirrhosis this system takes no part.

DISCUSSION

In summarizing the preceding factual summary, the following facts emerge:—

A. The outstanding events in acute parenchymal cellular necrosis are: (1) a very acute definitive onset; (2) immediate cellular necrosis beginning in the center of the lobule and proceeding outwards; (3) abundant evidences of inflammatory reaction and lymphatic involvement; (4) no involvement of the connective tissue stroma and of the reticulo-endothelial system; (5) full symptomatic and anatomical recovery in about one-half of the cases; (6) in the remainder continuing evidence of hepatic parenchymal disease; and, (7) in a very few, eventually some form of cirrhotic change.

B. The outstanding events in chronic parenchymal cellular disease are: (1) a clinically unrecognizable onset; (2) a state of general inanition of moderate to severe grade; and (3) wide spread cellular degeneration. There is a relatively normal lobular architecture. No further data are known concerning the early stages of this lesion, and we are unable to tell whether any lymphatic involvement is present.

C. In cirrhosis—chronic interstitial hepatitis—all of the known factors in group B are present plus (1) a chronic progressive fibrosis of the interlobular stroma; (2) atrophic destruction of the parenchymal cells beginning at the periphery of the lobule and progressing towards its center; (3) an otherwise relatively normal lobular architecture; (7) a non-involvement of the intralobular framework and the reticulo-endothelial system; and (8) no demonstrable evidence of any acute inflammatory reaction or lymphatic involvement.

In integrating these groups of facts, it seems important to examine the status of the lymphatic apparatus of the liver. The following resume is taken from Tobias (29).

The deep lymphatics of the liver form a network in the interlobular connective tissue which surrounds the lobule. The perilobular network is prolonged into Glisson's capsule, around the ramifications of the portal vein, hepatic artery and the biliary ducts. There is

also a lymphatic network on the hepatic veins which anastomoses with the lymphatics which surround the branches of the portal vein (Lee) (19).

The older belief of Teichmann (28), MacGillavry (21), Kisselew (18), von Wittich (31), Fleischl (10), Budge (4), Disse (8), Brissaud (3), etc., that the lymphatic paths of the liver originate in the hepatic lobules has definitely been disproved. The more recent researches of Herring and Simpson (14), Lee (19), and of Gabrielle (13), however, have conclusively proved that true lymphatics, i.e., vessels possessing an endothelial wall, do not extend beyond the interlobular spaces or crevices.

In other words, there is no lymphatic apparatus, as such, within the liver lobule. The only recognizable lymphatic plexus is in the interlobular stroma.

In the acute cases, there is abundant proof of the existence of an acute lymphangitis in the acute inflammatory reaction and in the presence of the acute lymphadenitis in the appropriate groups of glands. Undoubtedly the lymphatic vessels in the liver are equally involved. It seems safe to assume that the continuation of this process, or, at least, its incomplete retrogression to the normal, provides a pathological-anatomical basis for the continuance of the symptomatology in so many of the cases which recover from the primary illness, and which have come to be known as cases of chronic parenchymatous hepatitis or latent hepatic disease.

In cirrhosis, there is no such demonstrable evidence of previous acute lymphatic involvement. Nevertheless, the bulk of the lesion lies exactly in the location of, and parallels the lymphatic channels in the interlobular stroma. There is definitely no connective tissue, or other fibrotic change within the lobule, in which there are no lymphatic vessels, and in which stroma has been replaced by the elements of the reticulo-endothelial system and the sinusoids. The latter plays no part in cirrhosis.

Those very few cases of cirrhosis, which have been reported to have followed a very few of the acute cases of hepatitis, are found not only to have the same location in the interlobular stroma, but to also parallel the same lymphatic channels. In addition, there is the evidence of lymphatic involvement in the early stage of the illness, and the possibility of its incomplete retrogression.

By the essential nature of the lesion, by its position only in the interlobular septa, by the preceding presence of a definite lymphatic involvement at a prior observable stage in some of the cases, and by its intimate anatomical relation to the only situation where lymphatic channels are present, one must accept the lymphatic apparatus as the one common denominator of the conditions summarized in this communication leading to cirrhosis or chronic interstitial hepatitis.

It seems difficult to avoid the conclusion, that chronic interstitial hepatitis, or cirrhosis as here defined, is the

result of a chronic lymphatic process in the lymphatic channels which lie in the interlobular stroma—a chronic lymphangitis. There seems to be a close relationship between this essential process and those other agencies summarized herein—before as having been previously commonly accepted as the cause of cirrhosis. Sometimes they are consequences of the original cause of the cirrhotic process, and then they enhance its effects. Commonly they are associated agents. In any event all of them are collaterally mutually adjuvant and supplementary forces; and, when once this sequence of events begins, all of these factors aid and abet one another to the full development of the cirrhotic lesion or chronic interstitial hepatitis.

We cannot be certain, but it seems that the cellular degenerative changes are relatively less commonly the continuation of an unresolved acute parenchymal disease. There is much more reason to believe that in cirrhosis, the cellular changes are most commonly secondary and associated effects of the primary cause and of the variety of associated agents which take part, and/or of the final lesion. Mechanistically, the cell changes are due to interference with the nutrition of the cell, to the toxic effect of any of the associated agents in this complex process, or to the mechanical effects of the progressive strangulation produced by the slowly contracting perilobular fibrotic tissue in the interlobular stroma. Of this important parenchymal degenerative change, the general inanition, which is always present, is both a cause and a direct result as well as an infallible indication. As so frequently seen elsewhere, a vicious circle is present.

One must also associate this parenchymal cellular change with the demonstrable hypoproteinemia which accompanies the general inanition. We are beginning to think that the effusion of fluid in the general abdominal cavity is a general nutritional oedema to the exclusion of, or in addition to any mechanical effects of any portal area obstruction.

SUMMARY

In the liver, the development of the chronic interstitial fibrosis which is characteristic of cirrhosis, occurs along, and is limited to the interlobular septa; in which location only, demonstrable lymphatic channels lie. The fibrotic lesion parallels these lymphatic channels accurately. The presence of acute inflammatory changes and lymphatic involvement in acute lesions which rarely demonstrably precede, or are more often associated with cirrhosis, and the fact that the fibrosis is not present elsewhere in the liver than where lymphatic channels are present, seems to make it correct to assume that a chronic lymphangitis is the essential underlying cause of the cirrhosis. Elements of the reticulo-endothelial system are not involved either in the liver or in the spleen. All of the previously assumed causes for the development of this lesion are sometimes

consequences of the original causal agent, or frequently only associated agents which mutually aid and abet one another and enhance the total effect to the full development of cirrhosis. The degenerative parenchymal cellular changes are the continuation of some preceding acute parenchymal disease or of some intercurrent associated similar acute episode; or they are

secondary effects of the diverse associated causology and of the pathogenetic mechanism. The general inanition causes and/or results bilaterally from interference with cellular function. The peritoneal effusions are evidences of a general nutritional oedema and result from the hypoproteinemia and general protein deficiency which accompanies the general inanition.

REFERENCES

1. Barker, M. H., Capps, R. B., and Allen, F. W.: Chronic Hepatitis in The Mediterranean Theatre. (Nov. 3) 1945, 129:653-659.
2. Blumer, G.: Infectious Jaundice in the United States, J. A. M. A., (Aug. 4) 1923, 81:353.
3. Brissaud, E.: Le réseau d'origine des lymphatiques du foie.—*Le Progrès médical*, 1909, no. 37, pp. 465-469.
4. Budge: Neue Mittheilungen ueber die Lymphgefäße der Leber.—*Bericht d. Königl. Sächsischen Ges. d. Wissensch.*, 1875, vol. XXVII, p. 161. (cited by Lee, 19).
5. Caravati, C. M.: Posthepatitis Syndrome, *South. M. J.* (May) 1944, 37:251.
6. Cockayne, E. A.: Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the liver. *Quart. J. Med.*, 1912-13, 6:1-29.
7. Dietrich, S.: Der sogenannte katarrhalische Ikterus und die Hepatitis epidemica. *Deutsche med. Wehnschr.*, 1942, 68:5-10.
8. Disse, J.: Ueber die Lymphbahnen der Säugethierleber.—*Archiv. f. mikrosk. Anat.*, 1890, Bd. 36, pp. 203-222.
9. Findlay, G. M., Martin, N. H., and Mitchell, J. B.: Hepatitis After Yellow Fever Inoculation. *Lancet* (Sept. 9) 1944, 2:340.
10. Fleischl, E.: Von der Lymphe und den Lymphgefäßen der Leber.—*Arbeiten aus der physiologischen Anstalt zu Leipzig*, 1874, vol. IV, pp. 24-37.
11. Follows, A. B.: Epidemic Catarrhal Jaundice. *M. Officer* (Jan. 20) 1940, 63:23. Edwards, L. R. H.: Outbreak of Epidemic Catarrhal Jaundice. *Brit. M. J.* (April 17) 1943, 1:474. Pickles, W. N.: *Epidemiology in Country Practice*. Baltimore, Williams and Wilkins Company, 1939, p. 59. Ford, J. C.: Infective Hepatitis (Epidemic Catarrhal Jaundice): 300 Cases in Outer London Borough. *Lancet*, (May 29) 1943, 1:675.
12. Gaskell, J. F.: The changes in the liver and in a fatal case of epidemic "catarrhal" jaundice. *J. Path. & Bact.*, 1933, 36:257-262.
13. Gabrielle, H.: Le canal thoracique. Etude anatomique et expérimentale. *Imprimerie de Trevoux. G. Pattissier*, 1925.
14. Herring, P. and Simpson, S.: On the relation of the liver cells to the blood vessels and lymphatics.—*Proceedings of the Royal Society of London*, ser. B, 1906, vol. LXXVIII, pp. 455-496.
15. Kirk, R.: Spread of Infective Hepatitis. *Lancet* (Jan. 20) 1945, 1:80.
16. Klemperer, P., Killian, J. A., and Heyd, C. G.: The Pathology of "icterus catarrhalis." *Arch. Path.*, 1926, 2:631-652.
17. Kligler, I. J.: Btsh, D. S., and Koch, W.: Observations on Two Epidemics of Infective Hepatitis in Palestine Among Recent Immigrants, *J. Infect. Dis* (May-June) 1944, 74:234.
18. Kisselew, J.: Ueber die Lymphgefäße der Leber.—*Centralblatt f. d. mediz. Wissensch.*, 1869, vol. VII, pp. 147-148.
19. Lee, F. C.: On the lymph vessels of the liver. *Contributions to embryology*; Carnegie Inst. of Washington, 1923, vol. XV, pp. 65-71.
20. Lucké, Balduin: The pathology of fatal epidemic hepatitis. *Am. J. Path.*, 1944, 20:471-619.
21. MacGillavry: Zur Anatomie der Leber.—*Sitzungsber. d. Akad. d. Wiss. Wien*, 1864, Bd. 50, Abt. 2, p. 207 (cited by F. Lee, 19).
22. Molner, J. G., and Kasper, J. A.: An Outbreak of Jaundice in Detroit, J. A. M. A., (June 19) 1938, 110:2069. Molner, J. G., and Meyer, K. F.: Jaundice in Detroit. *Am. J. Pub. Health*, (May) 1940, 30:509. Norton, J. A.: Acute Infectious Jaundice. *J. A. M. A.*, (Sept. 2) 1939, 113:916. Symmers, D.: Epidemic Jaundice. Correspondence, *ibid.* (Dec. 18) 1943, 123:1066. Rogers, O. F.: Epidemic Hepatitis, Correspondence, *ibid.* (Dec. 18) 1943, 123:1066. Blumer (2).
23. Paul, John R., Major Havens, Jr. W. P., Lt. Col. Sabin, A. B., and Lt. Col. Philip, C. B.: Transmission Experiments in Serum Jaundice and Infectious Hepatitis, *J. A. M. A.*, (July 28) 1945, 128:911-915.
24. Personal communication to one of the authors (J. R. P.).
25. Polack, E.: Chronic Hepatitis in Young Persons With or Without Intermittent Jaundice. *Acta med. Scandinav.*, 1938, 93:614.
26. Stuhlfauth, K.: Group Outbreak Among Soldiers and Civilian Population in Norway. *Deutsche Militarärzt* (Oct.) 1941, 5:591; *abst.*, *Bull. War Med.* (Dec.) 1942, 3:213.
27. Siegmund, H.: Zur pathologischen Anatomie der Hepatitis epidemica (zuleich als Beispiel für die Grenzen der anat. Pathologie). *München med. Wehnschr.* (May 22) 1942, 89:463. Gutzeit, K.: Icterus infectiosus, *ibid.* (Feb. 20) 1942, 89:161; (Feb. 27) 1942, 89:185.
28. Teichmann, L.: Das Saugadersystem vom anatomischen Standpunkt, Leipzig, 1861.
29. Tobias, M. J.: *Anatomy of the Human Lymphatic System*. Ann Arbor Michigan, Edwards Brothers, Inc. 1938.
30. Turner, R. H., Snively, J. R., Grossman, E. B., Buchanan, R. N., and Foster, S. O.: Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine with especial consideration of severe attacks. *Ann. Int. Med.*, 1944, 20:193-218.
31. von Wittich: Ueber die lymphbahnen in der Leber.—*Centralblatt f. d. medicin.*
32. Wilensky, A. O.: The Importance of Latent Hepatic Disease. *Amer. J. Surg.*, (Sept.) 1944, 65:321-352.

Toxic Sulfonamide Colitis

By

HARRY GAUSS, M. D.*

and

L. J. WEINSTEIN, M. D.**

DENVER, COLORADO

THE COMMON toxic effects of sulfonamide therapy are well known and are supported by a generous literature. Other toxic effects are of lesser frequency and information concerning them is scant.

Among the common toxic effects are nausea and vomiting, jaundice and hepatitis, cyanosis, headache, dizziness, delirium, psychosis, drug fever, acidosis, dermatitis, anemia, leucopenia, leucocytosis, agranulocytosis, renal irritation, oliguria, hematuria, joint pains and arthritis, conjunctivitis and scleritis.

In the field of toxic digestive reactions, nausea and vomiting, jaundice and hepatitis have received considerable attention, while occasional reference is made to stomatitis and diarrhea which are considered to be rare complications.

Nausea and vomiting have received the greatest amount of study. These toxic manifestations are considered to be both local and central in their origin by Marshall and Long¹. The central origin has been demonstrated by inducing vomiting by the intravenous administration of sulfapyridine. The local origin is suggested by the observation of Haviland and Blake² who demonstrated that the vomitus contained a greater concentration of sulfapyridine than the blood. Likewise, Einsel³ and his associates have shown that following the intravenous administration of sulfanilamide, sodium sulfapyridine and sodium succinyl-sulfathiazole that these sulfonamides reached a much greater concentration in the gastric juice than in the blood, while with other drugs the concentration in the gastric juice did not reach the level of the blood. They consider significant the greater tendency of sulfanilamide and sulfapyridine to cause nausea and vomiting. Carryer and Ivy⁴, Cooke, Davenport and Goodman⁵ have also demonstrated that sulfonamides are excreted into the gastric juice. Einsel observes that sulfapyridine causes much greater nausea and vomiting than sulfadiazine when the same dose is administered.

Schiff⁶ observes that the peak concentration of the sulfonamides in the gastric juice is usually reached within 15 to 45 minutes after completion of the injection.

Regarding the jaundice and hepatitis which occur as toxic sulfonamide manifestations in the digestive tract, Garvin⁷ has reported four cases of toxic hepatitis which occurred during the course of sulfanilamide therapy. Three of the patients showed an associated exfoliative dermatitis with one fatality.

Watson and Spink⁸ have studied a large series of patients at the University of Minnesota and have come to the conclusion that the majority of patients receiving the usual therapeutic doses of sulfanilamide prescribed for severe infections show clinical or laboratory evidences of hepatic dysfunction. As a result of this liver damage, jaundice and hepatitis occur. At times the liver damage may be so severe that it results in lethal outcome. They have also observed that often there occurs a marked elevation in the urobilinogen content of the urine after sulfanilamide therapy which they regard as evidence of liver damage. Spink⁹ is of the opinion that it is possible that the incidence of cirrhosis of the liver may increase in the years to come because of the widespread use of sulfonamides.

Cline¹⁰ and Gertler¹¹ each report a case of acute yellow atrophy of the liver following the administration of sulfanilamide and prontosil respectively.

In the field of sulfonamide therapy of the digestive tract, a sulfonamide is desired which has a low absorbability from the gut in order to minimize the toxic effects of the absorbed drug. However, it must be borne in mind that this desired action is in direct contradistinction to that desired in the treatment of infectious processes where a high degree of absorbability is desired and which is necessary for the sulfonamide to reach the pathogenic organism which have invaded the tissues.

To meet the specific requirements of digestive tract therapy, sulfaguanidine was developed about 1940. It was supposed to have a low absorbability from the gut and hence exert a minimal toxic effect on remote tissues. However, it soon became apparent that this drug was likewise absorbed from the bowel in appreciable amounts. In 1944, Bunting and Levan¹² described their experience with sulfaguanidine in treating 191 ambulatory carriers of bacillary dysentery who were otherwise in apparently good health. They encountered a number of toxic reactions as fever, dermatitis, hematuria, crystalluria. These were of sufficient severity to necessitate discontinuing the drug in twenty patients. They concluded that sulfaguanidine therapy is not without its dangers.

In 1942 Poth¹³ and his associates introduced succinylsulfathiazole, commonly called sulfasuxidine, which they claimed is so poorly absorbed from the gut that only about five percent is excreted by the kidneys. Its action, therefore, approximates a local one in the gut. Sulfasuxidine has gained rapid favor in gastrointestinal therapy, and today is probably the sulfonamide of choice in the treatment of gastrointestinal in-

* Department of Medicine, University of Colorado.

** Formerly Major Medical Corps, Fitzsimons General Hospital, Denver, Colorado.

Submitted June 21, 1946.

fections because of its low absorbability. Yet even this preparation is not without its toxic manifestations. Pollard¹⁴ records his study of thirty-six patients of chronic ulcerative colitis treated by sulfasuxidine in the University Hospital at the University of Michigan. He observed one instance of increased number of stools, one of lymphocytosis and agranulocytosis, two developed erythema nodosum and one developed drug fever.

While sulfasuxidine is gaining favor in the treatment of gastrointestinal infections because of its low absorbability from the gut, this same low absorbability renders it ineffective for infections outside of the gut where a high degree of absorbability is necessary. Since most indications for sulfonamide therapy occur in infectious processes outside of the gut and in these cases a high degree of absorbability is desired, it is probable that toxic reactions will continue to be met in sulfonamide therapy.

In spite of the known facts that digestive complications are fairly common in sulfonamide therapy, including nausea, vomiting, hepatitis and jaundice, and that the absorbed sulfonamides are excreted into the digestive juices, little has been written on the toxic effects on the bowel. Yet, there is no apparent reason why this part of the gut should be exempt from the toxic effects of sulfonamide therapy.

It has been demonstrated numerous times that following the absorption of the sulfonamides into the blood stream, they are carried to the liver where they are partially conjugated into acetylated forms which are highly toxic. After again being thrown into the blood stream they are uniformly distributed throughout the body, also they are present in transudates and exudates. In dogs it has been demonstrated according to Long and Bliss¹⁵ that the sulfonamides are excreted into the saliva and pancreatic juice in addition to the gastric juice. Finally the sulfonamides are excreted in their free and acetylated forms in the urine in much the same manner as urea excretion, according to Smith¹⁶.

We have encountered three cases of toxic hemorrhagic colitis under varying circumstances which occurred during the course of sulfonamide therapy. The clinical symptoms and appearance of the colon were singularly alike in all three cases. We have been unable to find recorded instances of this type of toxic complication of sulfonamide therapy.

CASE REPORTS.

Case 1. Eddie K., a 27-year-old war worker, complained of a severe hemorrhagic diarrhea two weeks in duration. He was having 15 to 20 stools a day associated with severe abdominal cramps. The stools were dark and liquid in character and contained varying amounts of blood. He stated that he was nauseated and vomited. He had lost five pounds, he was tired, and felt weak and groggy. He had been taking six tablets of sulfathiazole a day for three weeks. He had been started on the sulfathiazole therapy by his physician for an upper respiratory infection. The physician had entered the military service and Eddie had just kept on taking the

six tablets of 7.7 grains of sulfathiazole daily, because he thought that it was the thing to do.

Examination showed an adult white male quite cyanotic, 27 years old, 5 feet 4 inches in height, weighing 157 pounds; his pulse was 125, his temperature was 97, his respiration was 18, his blood pressure was 100/54. His body habitus was of the strong muscular type, the conjunctiva were muddy in appearance. The eyes reacted sluggishly to light and accommodation. The throat was congested. The heart borders were normal, the tones were rapid, but clear, there were no murmurs. The lungs had good resonance, there were no rales and no rubs. The liver was palpable about a finger's breadth below the costal margin. There was diffuse tenderness over the entire abdomen and the descending colon was spastic, palpable and tender.

The urine was reddish brown in color with a specific gravity of 1032, strongly acid in reaction with a pH of 4.4, a trace of albumen was present, but no sugar. The sediment contained some W.B.C.s and some sulfathiazole crystals.

The blood contained 13 grams hemoglobin, 6,400 W.B.C.s; 3,800,000 R.B.C.s; Polys 55%; 42% Lymphs and 3% Transitionals. A single blood test for sulfathiazole was 8 mg. percent.

A sigmoidoscopic examination showed a granular swollen hemorrhagic mucosa to the full length of the 25 cm. scope.

The x-ray examination showed a highly irritable gastrointestinal tract. At six hours the meal was seen scattered throughout the colon which was markedly spastic and irritable. At twenty-four hours most of the meal had been evacuated, and the colon was highly spastic and irritable throughout its entire length. A barium enema was given which caused some discomfort. The colon filled well but was highly irritable and hypertonic throughout its entire length.

Liver function tests were not made.

Hospitalization was advised, but Eddie thought that he could carry on at home; so he was instructed to discontinue the drug at once, to remain in bed for the time being, to eat a bland diet and take aluminum hydroxide gel, a teaspoonful five times a day.

Eddie returned a week later to state that he felt fine, his diarrhea had stopped, his stools were normal, his color was good, and he had a normal healthy appearance.

Case 2. J. N., a 40-year-old male, was admitted to the hospital because of an evident lobar pneumonia of the right lower lobe. He had had a history of arrested pulmonary tuberculosis. Examination of the sputum showed the presence of pneumococcus type II and streptococcus viridans. He was given a total of twenty-two grams of sulfapyridine on the first two days of hospitalization, none on the third, and five more grams on the fourth day, making a total of twenty-seven grams of the drug. Blood concentrations of sulfapyridine were taken daily and reported as 8.4, 8.5, 4.3, 3.8, and 1.3 mg. The temperature on admission was 104. It dropped gradually by lysis reaching normal on the fifth day. On this day the patient developed a bloody diarrhea associated with severe abdominal cramps. His temperature rose to 102. The stools were liquid, frequent, painful and contained some blood. Mucus was not observed. A sigmoidoscopic examination showed a congested, swollen hemorrhagic mucosa to the full extent of the 25 cm. scope. Administration of the sulfonamide was discontinued and the patient showed rapid improvement. Within two days, his temperature again returned to normal and the diarrhea stopped with a complete cessation of the abdominal symptoms.

Case 3. A. M., a 21-year-old male, was admitted to the hospital with an evident lobar pneumonia of the right lower lobe. Examination of the sputum showed the presence of pneumococcus type III. He was given a total of twenty-two grams of sulfapyridine in the first three days. The blood concentrations of the sulfapyridine for the three days was reported as 6.3, 10.5, and 3.8 mg. The temperature dropped by lysis reaching normal on the third day. On the fourth day the temperature rose to 101, and at the same time he developed severe abdominal cramps and a bloody diarrhea. The stools were of frequent occurrence, liquid, and contained some blood. Sigmoidoscopic examination showed a swollen congested hemorrhagic mucosa to the full extent of the sigmoidoscopic. The patient also manifested nausea and vomiting. The sulfapyridine had been discontinued on the day of the onset of the bloody diarrhea, so no further procedure was necessary in his case. The diarrhea and cramps subsided completely within the next two days.

SUMMARY

THREE cases of toxic sulfonamide colitis are reported following the oral administration of sulfathiazole in one instance and sulfapyridine in two instances.

Although seen under different circumstances, the three patients presented singularly similar clinical pictures of the digestive tract complication. In all of them the colon was swollen and hemorrhagic to the

full length of the 25 cm. scope. The patients all had a severe diarrhea with frequent hemorrhagic stools associated with severe abdominal cramps.

With the withdrawal of the sulfonamides, the symptoms subsided, and the colon returned to its normal appearance; leading to the conclusion that the hemorrhagic colitis was the direct result of the toxic effect of the ingested sulfonamide.

REFERENCES

1. Marshall, E. K., and Long, P. H., J. A. M. A., 112, 1671, 1939.
2. Haviland, J. W., and Blake, F. G., Amer. Jour. Med. Sc., 199, 383, 1940.
3. Einsel, I. H., Nixon, E. N., Gitmann, L., and Rogoff, J. M., Gastroenterology, 1, 882, 1943.
4. Carryer, H. M., and Ivy, A. C., Jour. Pharm. Exp. Therap., 66, 302, 1939.
5. Cooke, M. Davenport, H. W., and Goodman, L. S., Yale Jour. Biol. and Med., 14, 13, 1941.
6. Schiff, L., Gastroenterology, 4, 3, 1945.
7. Garvin, C. F., J. A. M. A., 111, 2283, 1938.
8. Watson, C. J., and Spink, W. W., Arch. Int. Med., 65, 825, 1940.
9. Spink, W. W., Sulfanilamide and Related Compounds in General Practice, The Year Book Publishing Company, Inc., 1941. Chicago.
10. Cline, E. W., J. A. M. A., 111, 2384, 1938.
11. Gertler, W., Dermat. Wchschr., 107, 1020, 1938.
12. Bunting, J. J., Levan, N. E., J. A. M. A., 125, 773, 1944.
13. Poth, E. J., and Knotts, F. L., Arch Surg., 44, 208, 1942.
14. Pollard, H. M., Gastroenterology, 4, 4, 1945.
15. Long, P. H., and Bliss, E. A., The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds. The Macmillan Company, N. Y., 1939.
16. Smith, F. C., Sulfonamide Therapy in Medical Practice, F. A. Davis Co., Phila., 1944.

Simple Non-Sphincteric Localized Esophageal Spasm A CASE REPORT

By

MORRIS WEISS, Lt. COL.*

and

LEONARD LONG, Lt. Col.

MEDICAL CORPS, ARMY OF THE UNITED STATES

SPASM of the upper end of the esophagus (cricopharyngeal spasm) and of the lower end (cardio-spasm) are common entities. Spasm of the remainder of the esophagus is usually secondary to organic disease but simple non-sphincteric spasm does occur and McGibbon and Mather¹ in an excellent review and discussion state that it may be either localized or diffuse, the former type probably being the most common. Either type may occur in any portion of the esophagus and may be transient or prolonged, the cases of Moersch and Camp² having had symptoms varying in duration from two months to fifty years.

Although simple non-sphincteric spasm apparently is not frequently diagnosed, it probably is more common than the literature would indicate since the condition may be of very short duration and the symptoms too mild to require roentgenographic study.

It may occur in any age group and both sexes are equally affected. The exact etiology is still in doubt. Many theories have been advanced and it is felt by most observers that nervous instability plays an important role. However, reflex stimulation from lesions of thoracic or abdominal viscera may also be exciting factors²⁻³.

Either dysphagia or pain may be the outstanding symptom, the pain varying from a dull substernal ache to severe shooting paroxysms¹ and may lead to a di-

agnosis of angina pectoris².

The uncertainty and probable multiplicity of causes for simple non-sphincteric spasm would suggest similar uncertainty in results of treatment. Reports indicate this to be true. McGibbon and Mather state that all of the possible causative factors should be sought for in each patient and if found the appropriate psychological, therapeutic or surgical corrective measures can be adopted¹.

Roentgenoscopic and esophagoscopic studies make the diagnosis and differentiate it fully from dysphagia due to other causes, e.g., neoplasm, stricture and esophagitis.

CASE REPORT

A 29-year-old colored soldier, in the service for 28 months, was admitted to this military hospital the night of October 24, 1944, with complaints of inability to swallow and substernal precordial pain of a stabbing nature. History revealed an indefinite and unsubstantiated history of having swallowed lye at the age of five for which he received no medical care. Since then difficulty in swallowing has been present intermittently and required hospitalization one time before entering the army. One year ago it became increased in severity. He was observed in another military installation at that time and again 6 months later during another acute attack. Both times he was returned to duty following roentgenographic and esophagoscopic studies with a diagnosis of spasm of the esophagus, cause undetermined. He was then symptom free for a period of 5 months. On the day before admission to this hospital he suddenly developed another attack, the patient stating that the first mouthful of either solids or fluid lodged in his throat and prevented further swallowing. His last two attacks were similar and he stated that the attacks in service were more severe than those in civilian life. Physical examination on admission revealed a well-developed, well-nourished colored male 65 inches in height and weighing 154 pounds.

*Radiologist, Caylor-Nickel Clinic, Bluffton, Ind., on leave of absence.
Submitted June 18, 1946.

General examination was essentially negative. Blood pressure 154/76. Pulse 90. White blood cell count 7600, normal differential. Red blood cells 5,110,000. Hemoglobin 104%. Kahn negative. Stools and urine negative. Temperature normal.

The next morning the patient appeared fairly comfortable, not

parently as a result of his previous experience with this procedure elsewhere. He was persuaded to submit to the examination with some difficulty.

On November 3 an esophagosopic examination was performed with a No. 9-45 cm. instrument which could not be passed into the middle

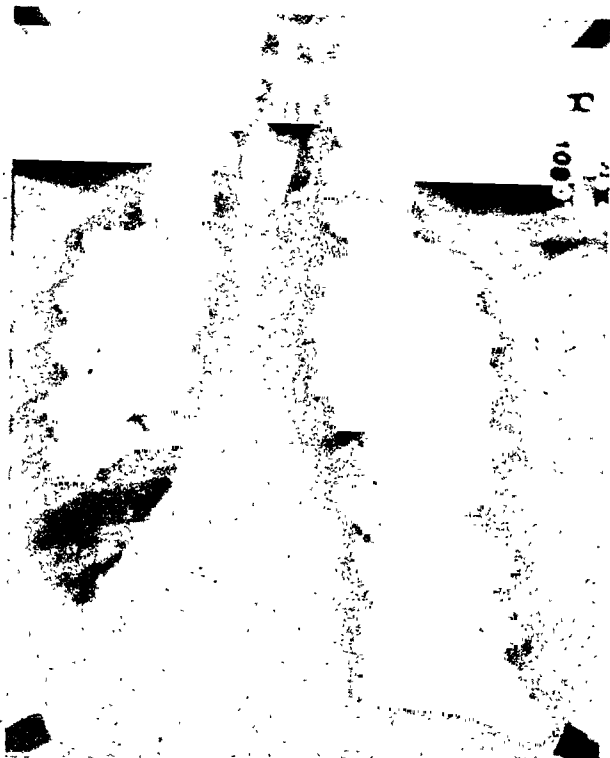


FIG. 1A

Fig. 1—(A) Esophagram a few hours after first admission showing complete obstruction at the level of T-2 and T-3. The irregular lower margin of the barium shadow simulates tumor but is actually produced by food lodged on the spastic segment. The rounded end



FIG. 1B

of the large barium capsule projects above the free barium. (B) Oblique projection reveals the true tapering contour of segment above spasm with filling defects due to food.

apprehensive, and was expectorating large amounts of saliva frequently. He appeared so comfortable that the validity of his complaints was doubted. On being given water to swallow he at first refused to attempt it. After considerable urging he took a single mouthful and tried to swallow it without success. He immediately was taken to the radiology department. Under roentgenoscopic observation the patient was able, with considerable difficulty, to swallow a small amount of barium paste. This barium stopped abruptly at the level of the disc space between T-2 and T-3 where the inferior margin of the barium shadow was slightly irregular with no visible tapering. A large capsule filled with barium was then administered and this lodged within the originally swallowed barium. None of the solution passed through the obstruction at any time during the approximately 15 minutes of intermittent roentgenoscopic observation. Films were then made which revealed that actually the lumen of the esophagus did taper above the obstruction, the barium having infiltrated slightly into a quantity of food material which was lodged upon the obstruction and outlined the true contour not visible roentgenoscopically. (Fig. 1.) After an interval of one hour another film revealed all of the barium in its original position.

The patient was given a liquid diet and gr. 1/150 of atropine sulphate administered every 8 hours. Within 24 hours he was able to swallow normally. The roentgenoscopic examination was then repeated on October 27 and the barium passed through the esophagus quickly with no evidence of obstruction, constriction, deformity or spasm at any point, including the cardiac sphincter.

The patient was then informed that esophagosopic examination was contemplated and he immediately became very apprehensive, ap-

third of the esophagus without undue force. No lesion was seen in the area visualized.

Two days later after intense sedation the esophagoscope was passed for its entire length without difficulty and an entirely normal esophagus was visualized. Following this the patient's symptoms completely disappeared. He was able to eat a regular diet and on November 9 was discharged to duty.

On January 20, 1945, he was again admitted with complaints of food lodged in his throat and inability to swallow. During the next 24 hours he refused everything by mouth and was given fluids intravenously. On January 22 roentgenoscopic examination was performed using a cotton pledget saturated with barium paste. This was held up at the level of T-1 and remained there until three hours later when it was observed esophagoscopically. About 5 hours following esophagosopic examination he began taking fluids well by mouth and one day later was on a bland diet.

On January 25 another esophagoscopy revealed a normal esophagus. The remainder of the patient's stay in the hospital was uneventful and on February 4 he was again returned to duty.

DISCUSSION

THE PATIENT's statement that he swallowed lye during childhood made it appear on admission that this was an organic stricture of the esophagus. The roentgenographic examination at this time seemed to support this. But the history of previous attacks with



Fig. 2—Normal esophagus 48 hours after admission.

asymptomatic intervening periods together with roentgenographic and esophagoscopy findings of obstruction that were transient in an individual with nervous instability indicates its functional nature. The lack of any evidence of organic disease, intrinsic or extrinsic, supports this impression.

This case is unusual in that the spasm is localized



Fig. 3—Second admission: Similar appearance as on first with barium saturated cotton pledget lodged above the spasm. It was still present here three hours later.

in the upper third of the esophagus but below the cricopharyngeus. The symptoms are very similar to those seen in cricopharyngeal spasm and differentiation from it or organic obstruction would be difficult without roentgenographic and/or esophagoscopy examination.

REFERENCES

1. McGibbon, J. E. G., and Mather, J. H., *Lancet* 1:1385 (June 12) 1937.
2. Moersch, J. H., and Camp, J. D., *Ann. Otol., Rhin. & Laryng.* 43:1165 (1934).
3. Teschendorf, W., *Ergeb. med. Strahlenforsch.*, 3:175 (1928).
4. Barsony, T., and Poegar, F., *Fortschr. Rontgenstr.*, 36:593 (1927).

A Modification of Plummer's Dilator for the Treatment of Cardiospasm

By

ERLING LUNDSTEEN, M. D.*
COPENHAGEN, DENMARK

THE BEST treatment of the so-called cardiospasm consists, as it is well known, in a forced dilatation of the narrow part. For this purpose several apparatus have been constructed; the one most frequently used is probably Plummer's dilator which has proved to be excellent in most instances.

Concerning the name of the disease it should be mentioned that the usual designation "cardiospasm" presumably is an unfortunate one. Thus Hurst is

of the opinion that the affection is an innervation disturbance which probably should be called cardiac achalasia, i.e., a failure to relax on the part of the opening. Others consider it a primary esophagus dilatation. But the narrow part is above the cardia, namely where the esophagus passes the diaphragm.

Even though the pathogenesis of the disease is not yet understood, it remains a fact that the treatment with dilatation is extremely effective.

Plummer's appliance consists, as is well known, of a rubber tubing which in its lower part changes into

* From the Bispebjerg Hospital, Medical Department B, Copenhagen. Submitted May 31, 1946.

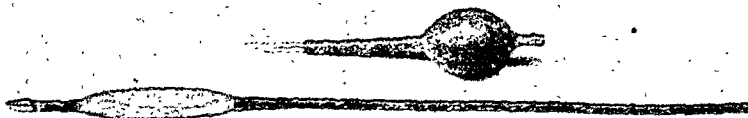
an oblong rubber balloon that can be inflated to a diameter of about 4 cm. In order to lead the apparatus through the narrow part in the esophagus a fishbone rod is placed inside the tubing to make this rather stiff. The tip consists of a metal head with a suitable perforation, the object being that the dilator in difficult cases may be lowered by means of a guiding wire which first has been swallowed by the patient.

After first having used Plummer's apparatus successfully in a number of cases we received a patient for treatment into whom it was completely impossible to introduce this dilator, even with use of the guiding wire. Roentgenology with a little contrast material in the esophagus showed plainly that the dilator, because of its rigidity, pushed the wall of the esophagus ahead so that a cul-de-sac was formed at the side of the esophageal hiatus. In this connection it may be mentioned that others, too, (Aage Nielsen) have described

inner pressure. The spiral is placed in the rubber hose.

It was extremely easy to introduce this dilator into our patient since it was soft and flexible so that it was pleasant to work with. During the last 10 years we have, therefore, used this appliance instead of Plummer's—much to the satisfaction of patients and physicians. The lower part is "soft and sensitive like a tapir's nose, so that one may ease its way forward without having the impression of using force" (Meulengracht).

At Bispebjerg Hospital, we always inflate the balloons by means of an ordinary rubber balloon (e.g., one used in a rectoscope). This is far more simple than Plummer's recommended distention by means of tap water with a manometer inserted to check the pressure. When inflating by means of air the pressure is, as mentioned, of no importance since it is lim-



Dilator and Rubber Balloon Used for Inflation.

cases where the ordinary Plummer dilator could not be introduced.

Hence, it was necessary to modify the apparatus, and we succeeded in two ways. In one the fishbone rod was replaced by a copper wire (diameter about 1 mm.). This made it possible to give the lower part of the dilator a suitable curvature (approximately as in a Mercier catheter) which made the introduction quite easy.

In the second modification, which proved to be the better one of the two, the copper rod was replaced by a steel wire spiral with a diameter of about 3.5 mm. (Spirals of this kind are, at least in Denmark, otherwise used as curtain rods for light curtains.) The apparatus consists of a rubber tubing of dimensions similar to those of an ordinary Ewald prober. At one end it is closed by a metal head, drilled through as in Plummer's dilator. Just above the metal head is the approximately 13 cm. long inflating balloon. The inside of this consists of a layer of rubber, then follows a silk-casing, and the outer layer is rubber. The silk has the importance that, like the canvas in an automobile deck, it prevents the inner rubber balloon from expanding beyond a certain limit, regardless of the

ited by the silk covering. It may be added that the inner rubber layer is more permanent when no water gets into the apparatus. It is our experience that a guiding wire never is needed when using this dilator.

It may be inconvenient in the dilatation of patients with cardiospasm that frequently some liquid is at the bottom of the esophagus. Hence Meulengracht recommends first to aspirate by means of a thin stomach-probe. This facilitates the following procedure, both for the patient and the physician.

Finally it must be mentioned that the modified Plummer's dilator described in this paper costs only about one-half of the original. (It may be obtained from the firm of Nyrop & Maag, Kobmagergade, Copenhagen.)

SUMMARY.

In a case of cardiospasm it was impossible to apply the ordinary Plummer's dilator. A modification was therefore produced which was easy to induce. It has a more suitable flexibility than the original one, for which reason it has for the last ten years been used in all patients with cardiospasm admitted to Department B of the Bispebjerg Hospital, Copenhagen.

BIBLIOGRAPHY

Hurst, H. S., and Rake, G. W., *Quart. J. Med.*, 23-491-1930.

Meulengracht, E., *Nordisk Medicin*. 29-263-1946.

Nielsen, Aage, *Ugeskrift for Læger*, 90-772-1928.
Plummer, H. S., and Vinson, P. P., *Med. Clin. North Amer.*, 5-355-1921.

Cancer of the Stomach

By

JOHN A. REED, A. B., M. D.*

WASHINGTON, D. C.

CANCER of the stomach is a curable disease. In making such a statement or in discussing this dread disease with such an approach, I recognize that there are sharp reactions varying from total non-believers to those who would like to feel that such is true but remain relatively skeptical. In studying cancer of the stomach, certainly there are those who approach the subject from a most pessimistic viewpoint and with a definite degree of justification but it has seemed to me that the subject might be developed from a more optimistic standpoint with a view to stimulating a keener interest and a more diligent search for the disease especially in its early stages, in a stage earlier than one usually finds at the clinical examination table. Let us therefore follow through with this optimistic approach and see whether it is justifiable and where it might ultimately lead in the future concerning it.

ETIOLOGY

Like cancer elsewhere in the human body, a specific cause is unknown. From all sources available it is felt that we must consider the etiology as not being due to one known specific factor, but probably many.

AGE FACTOR

No age is exempt but it is a disease of the individual well into adult life. Various ages have been given as being of the most common occurrence. Certainly we can say that more cancers of the stomach occur between the ages of 55 and 65 than at any other decade. Nettleship¹ has pointed out in an experimental approach to the production of cancer in the laboratory animal that the age factor is an important one. The mean age at the time of death from cancer among white persons has been given as 65 years².

SEX

Suffice to say it is more common in the male than in the female.

RACE

Cancer occurs in the white race twice as frequently as in the colored race. This is proven universally true and in a recent summary of the deaths from cancer of the stomach in the city of Washington, this prevails. This figure would naturally vary with the percentage of population of white and negro individuals within the various localities.

GEOGRAPHIC VARIATION

An interesting study has been presented by Collins, Gover and Dorn³ showing from a study of the 28 sites in the U. S. that the mortality rate from all cancers is definitely higher in the northeast, east, north, central and Pacific regions while the south and the rural plains and mountain states of the west, north and south central regions have lower rates. This geographic variance obtains likewise for cancer of the stomach.

ACHLORHYDRIA

An interesting observation has been made relative to the association of achlorhydria and gastric cancer aside from the actual destruction of hydrochloric acid producing glands. Brunschwig, Schmitz and Rasmussen⁴ state that there is evidence to indicate that the achlorhydria of cancerous stomachs is associated with a local concentration of a gastric secretory depressant which is demonstrated in extracts of achlorhydric cancerous stomachs and juices from such stomachs. Furthermore, the gastric secretory depressant was also observed in achlorhydric juices from a patient with pernicious anemia in incidents equal to that observed in achlorhydric juices from cancerous stomachs. I have not seen any observations relative to such a secretory depressant made in achylia such as the so-called functional achlorhydric individual but it would be an interesting study to have made.

OCCURRENCE

There are approximately 25,000 to 40,000 deaths reported to occur from cancer of the stomach each year in the U. S. The Bureau of the Census, Vital Statistics Division, for 1943 has given 25,720 deaths from cancer of the stomach. Undoubtedly this figure does not report the true occurrence of cancer of the stomach but only those cases wherein the attending physician felt that this disease per se was the direct cause or immediate cause of death. Undoubtedly, many more cases occur than are actually certified to in the usual manner. In the District of Columbia for the year 1945, there were 113 deaths from cancer of the stomach—this being a listing of the direct or immediate cause of death. This figure is very much lower than that for the country at large and estimated on the population would mean an expectancy of 13,000 deaths for the country at large. Livingston and Pack have graphically portrayed the occurrence of cancer from the standpoint of cause of death by a comparison of the three great causes of death namely war, highway deaths, and cancer of the stomach. They state that 15 years of war deaths amount to 244,357, 15 years

* Associate Clinical Professor, Department of Medicine, The George Washington University School of Medicine, Washington, D. C.
From the Department of Medicine, the George Washington University School of Medicine, Washington, D. C.
Submitted June 18, 1946.

of traffic deaths give a figure of 441,912 deaths, whereas 15 years of death from cancer of the stomach amount to 600,000. In the District of Columbia for the year 1945 there was a total of 113 deaths from cancer of the stomach and 99 deaths from motor vehicle accidents. If comparable publicity and effort as is made regarding prevention of traffic deaths were made in the prevention of cancer, our problem in this disease would make considerable progress toward substantiating the original thesis that cancer is curable.

POLYPS

The malignant potentialities of polyps of the stomach, I believe, no longer remain a question. Borrmann² has given adequate description of what is now generally recognized as malignant transformation of gastric polyps. The occurrence of cancer from polypoid growth varies from 1 to 3%. Schindler, who has made very accurate gastroscopic examinations, found that 2.9% of all gastric carcinomas, exclusive of cancer of the cardia, occur as a result of the malignant changes in gastric polyps. Gastric polyp, therefore, must be considered as a definite causative factor of gastric cancer and in itself has malignant potentialities always.

GASTRIC ULCER

For years the debate has gone on as to the relationship between gastric ulcer and gastric cancer. Authorities vary on the percentage of gastric ulcers which become malignant and the figure ranges from 10% to 80 odd percent of gastric ulcers becoming malignant. McCarty, many years ago, was misquoted as stating that 75% of all gastric ulcers become malignant. More conservative and accurate observations, however, are now at hand and the figure given ranges somewhere between 10 and 19%. The misunderstanding and the wide variation of the figures given by reliable authorities probably lies in the fact that those in lower percentage bracket mean that gastric ulcer of the benign nature later develop malignant changes whereas those of the higher percentage brackets have included what is considered malignant ulcers, or ulcers malignant from the start. Further debate on the relationship of gastric ulcer to cancer of the stomach seems to me to be without justification as will be pointed out and defined under treatment.

CHRONIC GASTRITIS

The relationship of chronic gastritis likewise as a precancerous condition has received its share of verbiage. Konjetzny, in 1913, stated that 85% of gastric cancers arose on the basis of chronic gastritis and that the latter constitutes beyond the shadow of a doubt a precancerous condition. Without further burdening the already overburdened literature on this debatable subject, four distinctly different conclusions are possible: 1. Many persons reaching the gastric cancer age have chronic atrophic gastritis, in other words, chronic gastritis is a process of ageing; 2. Chronic atrophic

gastritis precedes the development of gastric cancer; 3. Chronic atrophic gastritis is the direct result of cancer of the stomach; 4. The development of chronic atrophic gastritis is a nonspecific concomitant of many gastric lesions. If very early cancer of the stomach could be proved consistently associated with either the presence or absence of gastritis, the problem of relationship would be solved. Unfortunately, the material and observations are not at hand and reports are controversial. Certainly age is a factor in that as far as can be gleaned from the literature, no direct transformation from a truly non-malignant chronic gastritis has been observed to a malignancy comparable to that of a polyp:

HEREDITY

Heredity is an accepted factor in cancer of the stomach as well as cancer elsewhere in the body.

ENDOCRINE GLANDS.

Abnormalities of the endocrine glands have been considered to have an etiological relationship in the production of cancer. For instance, hyperthyroidism may cause either a hypochlorhydria or an achlorhydria.

According to Popoff⁶ injections of solutions of the post pituitary produces ulceration of the gastric mucosa while Schiffrin⁷ has shown that injections of parathyroid extract produce a decrease in the volume and acidity of the gastric contents. These observations might at least lead to further studies on the relationship of the endocrine glands to possible precancerous conditions in the stomach and ultimately assist in the possible prevention of the disease.

NEUROFUNCTIONAL FACTORS

Lesions of the mid brain have been known to produce gastric erosions in the experimental animal but they are only superficial erosions and not of a permanent nature. These factors are mentioned as stimulatory to further studies on cancer of the stomach.

SECRETORY STUDIES

Ivy's studies on the inhibitor of motility as well as the studies mentioned above of the demonstration of a secretory depressant of the gastric juices on patients with pernicious anemia certainly might lead to some speculation of the relationship to gastric cancer and further stimulate experimental work along this line.

DIET

Boyd, in his textbook on pathology, stated that cancer of the stomach was more frequent in individuals of a lower social stratum and suggested that the diet was different in the groups mentioned by him. Certainly hyperplasia and ulcers have been produced by deficiency diets and again are reported as a stimulant for further study. Hypoproteinemia is a common accompaniment of cancer of the stomach. 59% of gastric cancers have been shown to have hypopro-

teinemia. 86% of all gastrointestinal cancer was found to have a low plasma level of vitamin A. Specific observations of the production of ulcers and the maintenance of those experimentally produced ulcers by dietary deficiencies over a long period of time are not available at present but certainly such work should be carried out and attempts be made in the element of time which we so readily recognize as the age factor in human cancer of the stomach.

ALCOHOL

The role of chronic alcoholism in the production of chronic gastritis considered by many as a precancerous condition is still a matter of speculation and without exact factual proof.

BACTERIA, BACTERIAL PRODUCTS, VIRUSES, ALLERGY

It is known that certain bacterial agents produce achlorhydria and the relationship therefore of bacteria and bacterial agents as causative factors has been considered. Oberling⁸ has suggested that all cancers may ultimately be shown to be virus diseases. However, at present, it has not been possible to demonstrate a causal virus. Definite and exact experimental evidence is lacking concerning bacteria, bacterial agents, virus, and allergy.

PATHOLOGY SITE

Dividing the stomach into the pars pylorus, pars media and the cardia, the most frequent site of occurrence is in the pars pylorus, next the pars media and last the cardia. Alvarez quotes Welch's 1,300 cases with the distribution of the growth in the stomach as follows: Pyloric region, 791; lesser curvature, 148; cardia, 104; posterior wall, 68; the whole or the greater part of the stomach, 61; multiple lesions, 45; greater curvature, 34; anterior wall, 30, and fundus, 19. In substantiation of the opening statement that cancer is curable, keep in mind always that the pyloric region of the stomach is by far the most frequent site of the occurrence of gastric cancer.

TYPES

From the cellular standpoint, cancer of the stomach may be classified as follows:

1. Adenocarcinoma is the most common type. Microscopically this consists of tubular structures lined with cells which are distinctly abnormal. These cells break through the lining membrane and invade the surrounding tissues.

2. Medullary is the second group and appears as a soft, grayish, vascular mass which grows rapidly into all the coats of the stomach. They ulcerate easily and metastasize rapidly.

3. The scirrhus cancer is dense, hard and slow-growing. This may invade the entire muscle layer and become what is commonly called "leather-bottle" stomach.

4. The gelatinous or colloid cancer has a translucent appearance. Microscopically the epithelial tissues are replaced in large part by structureless gelatinous material. It spreads widely through all the coats of the stomach and into adjoining organs.

5. A squamous-cell carcinoma is sometimes found at the cardia, where it arises from esophageal epithelium.

The microscopic typing of cancers and the microscopic examination of cancers would perhaps have even greater value when biopsy by gastroscopic means is developed to better proportions.

MICROSCOPIC CLASSIFICATION OF CANCERS

Polypoid carcinoma. This is a sharply limited growth often looking like a mushroom with overhanging edge. Its surface presents numerous nodes and nodules which are of different size. Ulceration is a later stage. This type comprises 2.9% of all gastric cancers if the cancers of the cardia are omitted.

The second type is found in 17.6% of all cases. It is an ulcer surrounded by an elevated wall. This wall has a steep slope toward the surrounding mucosa and is sharply demarcated all around against the surrounding mucosa. This type develops metastasis only at a late stage and its removal may lead to an extremely good end result and to cures of long duration if the operation can be performed reasonably early.

The type three carcinoma is similar in some respects to type 2 except that the wall is found only at one side and bleeds diffusely at the other side and occurs in 16.3% of all cases.

Type four is the diffuse infiltrating type which unfortunately is seen in 63.2% of the cases of gastric cancer. There is no sharp limit anywhere between the normal mucosa and the diseased mucosa and sometimes the entire stomach may be infiltrated. This is an unfavorable type for management.

LONGEVITY OF GASTRIC CANCER

The duration of gastric cancer depends somewhat on the type and the inherent malignancy of the cell. In general, the longevity is less than one year from the onset of symptoms to death. However, instances are reported of much longer duration. Palmer⁹ reports a case gastroscopically and roentgenically studied with a duration of 4 years proven and if the history of "indigestion" is indicative of minimal symptomatology, the total duration of his case would be 8 years.

Schwartz¹⁰ reports a case in which metastatic carcinoma was demonstrated in the bone marrow 3 years before death and concludes that the attitude toward surgical intervention in the presence of metastases may bear reevaluation.

Feldman¹¹ cites a case that had been studied from 1925 to 1942, duration of 17 years which eventuated in an operation and an inoperable carcinoma was found and suggests that the persistent prepyloric roentgeno-

logical narrowing should always be considered as having clinical significance. Feldman likewise reports a case of 3 years' duration and one of 6 years' duration from the standpoint of symptomatology.

SPREAD AND METASTASES OF GASTRIC CANCER

Gastric cancer spreads and metastasizes by: 1. direct growth, 2. The lymphatics, 3. The blood stream. The direct growth is to duodenum, esophagus, the gastrohepatic and gastrocolic omenta, pancreas, diaphragm, transverse colon and the liver. It spreads by the lymphatic to the lymph nodes along the greater and lesser curvature and later to distant lymph nodes. The blood stream spread is first to the liver and later other parts of the body. 10½% of autopsy groups show no metastasis. The liver was found to have growths in 50% of the cases, peritoneum, omentum and mesenteries in 42.6% of the cases, the lungs and pleura 32.8%, the ovaries 14%, and the bones 11.2%.

SYMPTOMATOLOGY

For years many of us have been lecturing in the classroom and giving as the characteristic symptomatology of gastric cancer, pain in the pit of the stomach, vomiting of coffee-ground material, emaciation, palpable mass in the upper abdomen, achylia, the presence of blood in the gastric contents and in the stool, and marked secondary anemia, as the characteristic textbook picture or classic symptomatology of gastric cancer. Without evasion of our responsibility in our lectures to students, one might say that this is a natural thing to have done since the vast majority of cases of cancer of the stomach come to the physician with just such symptomatology. Whereas, this symptom group is not necessarily the symptomatology of gastric cancer but the symptomatology of its late phase.

What then are the early symptoms of gastric cancer which may be of value in effecting cures and reducing the mortality rates in this disease?

Actually there are no characteristic pathognomonic signs or symptoms which lead one to establish an early diagnosis and because of this, places upon the physician a sharp responsibility of being constantly on the alert attempting to ferret out the early phases of the disease. Surely, one can say that any symptomatology referable to the stomach should be considered by the physician as a possibility of malignancy of that organ until irrefutably proven otherwise. The appearance of any epigastric distress, anorexia, heartburn, nausea, vomiting, easy fatigability, loss of weight or in brief any symptom referable to the stomach not previously present in any individual should be looked upon with suspicion. Apparent trivial remarks as to the causation by the patient must not be taken lightly or overlooked by the physician. Not infrequently the individual will say that he has not felt well since such and such a date when he took a cold bottle of beer, or that he has not been well since such and such a time when he ate a

large meal, or that he has not been well since he ate a particular kind of food. The patient will not infrequently time his symptomatology from an unrelated illness such as a severe cold or an attack of "flu." Such statements on the part of the patient must be considered as important by the physician and not dismissed lightly.

Boyce¹² summarizes the responsibility of the physicians as a three-fold task: 1. The physician must interpret all symptoms presented while rather still obscure. 2. The physician must abstain from medical treatment of so-called indigestion or ulcer until he is absolutely certain without any question of a doubt of his diagnosis. 3. The physician must reduce the interval between the time he sees the patient and the time the surgeon operates on him.

It is not infrequent that a physician, in all good faith, may make a diagnosis of gastric ulcer with not only the symptomatology more or less characteristic but supported by x-ray evidence of such, only later to find that the patient is developing a palpable mass in the epigastrium. One must not be led into the false security of having a patient with varying and obscure symptomatology respond to medical management of peptic ulcer and be informed by the patient that he is now well, only later to discover that the obscure symptomatology was the early signs of a gastric ulcer and that the roentgen analysis failed in its interpretation.

We are well aware that the patient himself fails to consult any physician until he has an inoperable situation and therefore mass education concerning cancer of the stomach should be as extensive as that now promulgated for such diseases as tuberculosis and syphilis. It is likewise true that digestive symptoms are at times completely lacking or are so slight as to not make the individual aware of his digestion and are only elicited upon leading questions. The symptomatology of cancer may develop abruptly with vomiting or hematemesis and be beyond the reach of surgical intervention. In regard to symptomatology, therefore, in summary I would ask that the physician keep in mind, and I repeat for emphasis, that any symptom referable to the stomach should be considered as an "obscure" or early sign of gastric cancer. This would be particularly true in an individual who had otherwise been free of digestive complaint and doubly true if over the age of 40.

DIAGNOSIS

The diagnosis in the advanced phases presents little or no difficulty. The presenting symptoms of pain in the stomach, nausea, vomiting, severe emaciation, marked secondary anemia, a palpable tumor, blood in the gastric contents and stool, an achylia, and roentgen studies make the diagnosis. Therefore, we can state generally that the diagnosis of cancer of the stomach is based upon the symptomatology, the physical findings, and certain laboratory findings.

As indicated under "Symptomatology," the diagnosis

of early carcinoma of the stomach is difficult. As far as symptomatology is concerned, we can only once again state that vague gastric or gastrointestinal symptoms should arouse in the mind of the examining physician the suspicion of cancer and no stone should be left unturned until cancer of the stomach is ruled out.

X-RAY FINDINGS

X-ray examination is the chief method for the recognition of gastric carcinoma and I simply want to point out a few of the pitfalls in this procedure, as well as a few suggestions to keep in mind. A certain percentage of errors will occur and the method should not be condemned because of these errors. Less than 1% errors occur in this method of examination. A negative x-ray diagnosis must not be taken as conclusive evidence that cancer does not exist. If we keep this in mind, surely the physician will continue to search for the disease. Further, one single positive evidence should not stop our search for further confirmation. Kirklin¹³ has stated that one error which is utterly indefensible is the failure to discover any existing gastric cancer, whatever its size, situation, or morphologic characteristics may be. Such an error should be charged to the examiner and not the method. Often a cancer of the cardia will not be discovered unless the region of the gas bubble is inspected closely. Schindler¹⁴ has suggested a relief method which consists of filling the stomach with a very thin layer of barium, compressing the stomach and taking spot films in the suspicious regions which will be helpful especially in small lesions in the region of the cardia. It has been stated that ulcer niches more than 2.5 cm. in width should be always considered as malignant conditions. The characteristic filling defect deformity on x-ray films is almost a pathognomonic roentgenological finding. Feldman has stated that the demonstration of a persistent narrowing of the pylorus should lead one to suspect a possible lesion in this region. The hour-glass stomach frequently seen in both ulcer and cancer can be differentiated many times by the fact that the barium stream in the cancer case is in the middle of the two lobes, while the barium stream in the ulcer case is usually along the lesser curvature. Interference with the normal peristaltic wave on roentgen study is considered a definite evidence of a lesion. In regard to cancer of the cardia, films should be taken in every possible position, namely standing, recumbent, right and left oblique and in the Levy Dorn position, that is, with the patient in the supine position, buttocks elevated, and the rays directed to the cardiac bubble. Deformity of the air bubble in the cardiac region should lead one to suspect a lesion in this area. One of the most frequent sites overlooked on the roentgen examination of cancer is where the lesion invades the posterior wall without the invasion of the anterior wall or the curvatures. Evidence of pyloric obstruction is determined by the presence of barium

remaining in the stomach five hours after ingestion of the barium.

GASTROSCOPIC

The debate which has taken place for a number of years as to whether the x-ray or gastroscopic examination is of more importance is in reality nonessential and should cease. Gastroscopic examination of any case not clearly diagnosed otherwise always should be made. Limitations: Those cases that present obstruction at the cardia may prevent the examiner from introducing the gastroscope. Necrotic material, blood or barium sulfate may obscure the visibility in the presence of pyloric obstruction. There may be no visibility in the linitis plastica type of cancer owing to the inability of the stomach to inflate. Lesions may be overlooked in the so-called blind areas in the gastroscopic examinations. These blind areas comprise a part of the cardia, part of the fundus, the upper part of the lesser curvature, the upper part of the posterior wall, the lesser and posterior wall of the antrum, and part of the greater curvature where the tip of the instrument impinges on the gastric wall. In spite of these limitations, gastroscopy may be of great value in the diagnosis of gastric carcinoma. Both methods, x-ray and gastroscopy, should be used and improved percentages of diagnoses can be brought about by such use. No individual unfamiliar or untrained in its use and untrained in the findings of gastroscopic examination should attempt its use.

GASTRIC ACIDITY

We are usually under the impression that gastric cancer presents either a sub acidity or an anacidity. The determination of the gastric acids, of course, is of some value but they can not be regarded as pathognomonic of the exact condition of the lesion present. In one study¹⁵, 11.4% of the cases of gastric acidity were found to be within normal range. In 28.5% it was subnormal, and in 60% there was no free acid. Occasionally, and this must be remembered, an ulcer will reveal no acidity likewise.

ANEMIA

It must be kept in mind that gastric cancer may be present without evidences of a lowering of the hemoglobin or red cells.

OCCULT BLOOD

Occult blood in the stool or gastric aspirations normally thought to be indicative of the presence of a lesion in the gastrointestinal tract may be absent in one or both in gastric carcinoma.

In summary, a good clinician will not be swayed easily by laboratory tests when they run counter to his clinical judgment. At present, all laboratory tests should be evaluated for what they are worth and no more. They have far greater positive than negative value.

DIFFERENTIAL DIAGNOSIS

One of the most difficult problems is the differential diagnosis between a benign gastric cancer and one which is malignant or a benign ulcer which has become malignant. The highest court of appeal in assisting in this differential diagnosis is the microscope and therefore the question naturally arises as to the therapy of the gastric ulcer. I will speak of this under "treatment."

PROGNOSIS

The prognosis of gastric cancer is certainly in all cases to be guarded. Here again generally we are led to believe that the prognosis of gastric cancer is exceedingly grave and, of course, this is the result that we only too commonly see in gastric cancer in its last phases. Surely, if gastric cancer is early diagnosed, is of a relatively low malignancy according to the Broder's classification, its site one that lends itself to resection namely in pyloric region, and metastases absent, the prognosis should be improved over that which we commonly feel. Every large institution should have in its gastroenterological section, a specific setup for the study of gastric cancer. A gastric cancer clinic, such as has been established in a number of leading institutions in the country with definite set approach to its study, will offer much in the importance in the prognosis of this disease. A gastric cancer team consisting of well-trained competent gastroenterologists, a surgical team capable of competent gastric resection, trained radiologists, and trained gastroscopists should be the basis of improvement in the outlook of this disease. Statistical studies show an ever improving number of 3 year, 5 year, 10 year, and even more cures in this disease. While the immediate surgical mortality of gastric resection remains high, statistics show that 1 in 4 persons¹⁶ have some chance of a definitive cure. Livingston and Pack¹⁷ in an excellent treatise state that the resectable case is 1 in 5. They point out that the figures of 1 to 5% of definitive cures is an error in that this includes all cancers, but, if we study those cases who have resectable cancers, and this reaches as high as 37% in some groups, 20% of the resectable cancers show a definite cure of 3 years or longer. A definitive cure should take into consideration the expected longevity of the individual at the time of his operation and if this is done, keeping in mind that the individual at a given age has a certain individual longevity, definitive cures may reach as high as 50%. The total number of resectable cases of cancer of the stomach exceed that of cancer of the lip, larynx, thyroid, vulva, skin and penis. Livingston and Pack report 25% of resectable cancer live 3 years, 18.5% live 5 years, and 10.7% live 10 years or more.

TREATMENT

Treatment of gastric cancer is surgery and the surgical procedure to follow is resection whenever possible. Resection of the stomach, therefore, is the treat-

ment of gastric cancer. One must remember that cancer of the stomach is fatal 100% without resection and no resection means no cures. The operative mortality of gastric cancer still remains exceedingly high and Livingston and Pack have reported that in 12,000 cases of malignant tumors of the stomach, of those having resection operations there was a 25% surgical mortality. The surgical mortality has improved. From 1900 to 1925 the operative mortality was 36%, whereas from 1925 to 1935 it was reduced to 25% and in recent years the average operative mortality rate has been in the neighborhood of 17%. In the "Report of Surgery of the Stomach and Duodenum for 1944 at the Mayo Clinic"¹⁸ 60% of the patients upon whom a diagnosis of malignant lesions of the stomach was made at the clinic in 1944 were treated surgically. There was a total of 298 malignant cases, ten of which were sarcoma. 172 of the 298 cases had a resection, or a resection rate of 57%. The mortality rate in the partial gastrectomy cases which consisted of 151 cases of the total 172 resections was 5.3%. In 21 patients who had a total gastrectomy, the total hospital mortality rate was 47.6% which is about twice the mortality rate usually expected for this operation but this rate is not particularly surprising when it is known that several of the patients who died, had in addition to the entire removal of the stomach, resections of portions of the pancreas and transverse colon. St. John, Swenson and Harvey¹⁹ reported a mortality rate for the period of 1908 to 1937 of 33.8%; for the period 1933 to 1942 a mortality rate of 17.9% and a mortality rate for the year 1942 of 4.7% in resections for carcinoma of the stomach. Even the resection for carcinoma involving the cardia and lower portion of the esophagus is now being done with surprisingly good results. Clagett at the Mayo Clinic²⁰ reported 27 cases of transthoracic resection of the cardia and lower portion of the esophagus for carcinomas arising in the cardia and three cases of resection for carcinoma arising in the esophagus. In the last 18 resections done, there was not a death. Surely when this otherwise fatal condition can now be approached surgically with the hope of cure, one is justified in being optimistic about this disease rather than pessimistic.

Even the question of the presence of metastasis should certainly be somewhat revised in view of the fact that it has been demonstrated that a given number of patients remain alive with resection for some years even in the presence of metastasis. The presence of metastasis, therefore, should not dogmatically mean "no operation."

I cannot at this time but help mention the question of surgery for gastric ulcer. Allen and Welch²¹ follow a conservative and probably middle-ground surgical approach and lay down rather definite rules as to whether a gastric ulcer should be operated upon but when one knows that the microscopic examination is the only way to determine malignancy of an ulcer,

one feels like having a more drastic approach and operating on all gastric ulcers—a resection.

In conclusion may I say that I for one earnestly and sincerely adhere to the philosophy of first, surgical exploration of every case of cancer of the stomach even though all diagnostic measures available point to an inoperable situation. Secondly, I adhere to the phil-

osophy of gastric resection wherever possible even in the presence of metastasis if such resection is not anticipated to cause the immediate death of the patient because of concomitant conditions. Thirdly, I adhere to the philosophy of resection of gastric ulcer even though our present clinical diagnostic measures suggest a benign nature of this ulcer.

REFERENCES

1. Nettleship—Arch. of Surgery, June, 1943, Vol. 46:793.
2. Cancer Mortality in the U. S. Public Health Bulletin 275, 1941.
3. Collins, Gover & Dorn—J. Natl. Cancer Inst., Vol. 1, No. 4, Feb. 1941.
4. Brunschwig, Schmitz & Rasmussen—J. Natl. Cancer Inst., Vol. 1, No. 4, Feb. 1941.
5. Borrmann—Handbuch der Speziellen Pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, Vol. 4, pt. 1, pp.812-1054.
6. Popoff—Arch. of Path. 31:220, Feb. 1941.
7. Schiffrin—Am. J. Physiol. 135:1942.
8. Oberling—The Riddle of Cancer, Yale University Press, 1944.
9. Palmer—Gastroent. Vol. 1, 1943.
10. Schwartz—Arch. Int. Med. Vol. 22, May 1945.
11. Feldman—Gastroent. Vol. 2, 1944.
12. Boyce—J. A. M. A., Vol. 117, Nov. 15, 1941.
13. Kirklin—Arch. of Surgery, Vol. 46, 1943.
14. Schindler—J. of Natl. Cancer Inst. Vol. 1, Feb. 1941.
15. Reid—Journ. Natl. Cancer Inst. Vol. 1, Feb. 1941.
16. Walters, Gray & Priestley, Arch. of Surgery, Vol. 46, June 1943.
17. Livingston & Pack—Treatment of Cancer, Hoeber, 1939.
18. Proceedings of the Staff Meetings of the Mayo Clinic, Vol. 21, No. 1, Jan. 9, 1946.
19. St. John, Swenson & Harvey—Annals of Surg. Vol. 119:1944.
20. Clagett—Proceedings of the Staff Meetings of the Mayo Clinic, Vol. 20, No. 26, Dec. 26, 1945.
21. Allen & Welch—Annals of Surgery, Vol. 114, 1941.

Effects of Polysaccharides on the Appetite and Efficiency of Food Utilization in the Growing Rat.

By

B. H. ERSHOFF, Ph. D.*

and

H. B. McWILLIAMS, B. Sc.

LOS ANGELES, CALIFORNIA

THE PURPOSE of the present communication is to report the effects of polysaccharides on the appetite and efficiency of food utilization in the growing rat. The polysaccharides employed consisted of cellulose², agar agar³ and pectin⁴.

Thirty female rats of the Long-Evans strain were selected for the following experiment at 23 to 25 days of age and an average weight of 42.7 grams. Animals were placed in individual metal cages with raised screen bottoms to prevent access to feces, and feeding was continued for eight weeks. Diets listed in table 1 were fed ad lib, and records were kept of the daily food consumption of all rats.

Results are summarized in table 2. Rate of growth, gross appearance and caloric consumption on diet A was not inferior to that observed on the polysaccharide-containing rations. On the contrary, growth was somewhat depressed on the agar agar and pectin-containing rations, and at least for the latter the reduction appears significant. Depression in growth was correlated not only with reduced caloric intake but also with reduced efficiency in the utilization of ingested calories. Of the three polysaccharide-containing rations, that containing cellulose was the

TABLE 1
COMPOSITION OF EXPERIMENTAL DIETS

	A	B	C	D
Vitamin Test Casein ¹	30.0	30.0	30.0	30.0
Salt Mixture ²	4.5	4.5	4.5	4.5
Yeast ³	12.0	12.0	12.0	12.0
Cottonseed Oil ⁴	10.0	10.0	10.0	10.0
Sucrose	43.5	33.5	33.5	33.5
Cellulose (Cellu Flour)		10.0		
Agar Agar			10.0	
Pectin				10.0

To each kg. of the above diets were added 1.2 grams choline chloride and 5 mg. 2-methyl-naphthaquinone. Each rat also received a weekly supplement of a vitamin A-D concentrate⁵ containing 100 U. S. P. units of vitamin A and 10 U. S. P. units of vitamin D.

¹General Biochemicals, Inc., Chagrin Falls, Ohio.

²Salt Mixture No. 1 (Sure (1).)

³Brewers' Type Yeast No. 200, Anheuser-Busch, Inc., St. Louis, Mo.

⁴Wesson.

⁵Nopco Fish Oil Concentrate, assaying 800,000 U. S. P. units of vitamin A and 80,000 U. S. P. units of vitamin D per gram.

most satisfactory from the standpoint of growth, caloric consumption and efficiency of food utilization. It is not improbable that under the conditions of the present experiment the poorer performance of the agar agar and pectin-containing rations may have been due in part to the greater affinity of these substances for water with a resulting decrease in the absorption and utilization of water soluble nutrients.

* From the Emory W. Thurston Laboratories, Los Angeles, California. Submitted June 24, 1946.

TABLE 2
EFFECTS OF POLYSACCHARIDES ON FOOD INTAKE AND
EFFICIENCY OF FOOD UTILIZATION FOR GROWTH
IN THE RAT

Group	Number of Animals	Initial body weight (grams)	Average gain in weight for 8 week per- iod ¹ (grams)	Calorie value per gram diet ²	Average food intake per rat for 8 week period		Average calorie intake per gram gain in weight.
					Grams	Calories	
Diet A	6	41.0	157.0 ± 5.8	4.33	577.8	2495.1	15.62
Diet B	8	43.0	125.0 ± 6.0	3.92	601.0	2543.4	17.61
Diet C	8	42.5	117.7 ± 11.2	3.92	545.7	2295.0	19.61
Diet D	8	42.6	113.6 ± 3.6	3.92	550.2	2196.0	19.33

1. Including standard error of the mean calculated as follows:

where "d" is the deviation from the mean and
"n" is the number of observations.

$$\sqrt{\frac{d^2}{n}} / \sqrt{n}$$

2. Computed on the basis of 4 calories per gram protein or car-
bohydrate and 9 calories per gram fat. It is assumed that cellu-
lose, agar agar and pectin yield no calories to the organism.

SUMMARY

Female rats were raised to maturity on a poly-
saccharide-free diet and rations containing respectively
10% cellulose, 10% agar agar and 10% pectin. No
beneficial effects on growth, gross appearance, appe-
tite or efficiency of food utilization were observed on
any of the diets due to the presence of the respective
polysaccharides.

1. The subject matter of this paper has been undertaken in co-
operation with the Quartermaster Corps Committee on Food Re-
search.
2. Cellu Flour, Chicago Dietetic Supply House, Chicago, Ill.
3. Bacto-Agar, Difco Laboratories, Detroit, Mich.
4. N. F. Pectin, California Fruit Growers' Exchange, Ontario, Calif.

BIBLIOGRAPHY.

- (1) Sure, B.: Dietary requirements for fertility and lactation XXIX.
The existence of a new dietary factor essential for lactation.
J. Nutrition, 22:449, 1941.

Gastragogue Effect of Laxatives and Allyl-Bromide-Mixture*

By

HENRY M. FEINBLATT, M.D.

and

EDGAR A. FERGUSON, JR.**

BROOKLYN, N. Y.

THE NAME "Gastragogue" has been adopted to des-
ignate a substance that aids in emptying the stom-
ach of its contents. The word is derived from the
Greek gastr-gaster, meaning "the stomach," and the
Greek agog-agoge, meaning "a carrying away or lead-
ing away."

Although it has been repeatedly tested pharmacody-
namically and proven that laxatives have little or no
effect on any but the muscle of the bowel, it is usually
believed that the stomach emptying time is decreased
by administration of a laxative.

In an effort to learn whether laxatives did, in fact,
help empty the stomach, the effect of a mixture of
Emodin cathartics with phenolphthalein was employed
in cases of six-hour retention associated with symptoms
of gastralgia after meals.

CONSTANCY OF 6 HOUR BARIUM RESI- DUUM BEFORE AND AFTER ADMINIS- TRATION OF LAXATIVE

In order to determine whether or not the barium
residuum was constant with two different administra-
tions of the barium meals on different days, a series of
cases was studied in whom the barium meal technic

was unchanged, except for the administration of lax-
atives during the second series to each of the following
patients:

Case No.	Age (Yrs.)	Height (Inches)	Weight (Pounds)	Sex
6	42	66	126	M
10	34	68	132	F
11	46	62	125	F
14	37	65	128	F
17	36	63	132	F
20	42	66	144	F
21	40	68	146	M
Average	39.9	65.4	133.3	

These patients had the following symptoms, and the
diagnosis was:

Case No.	Anorexia	Nausea	Vomiting	Belching	Diagnosis
6*	X			X	Duodenal ulcer constipation
10*					Duodenal ulcer
11*	X				Duodenal ulcer
14*					Duodenal ulcer
17*		X		X	Duodenal ulcer
20	X			X	Duodenal ulcer
21					Gastralgia and constipation

*See case number in Allyl-bromide-mixture series.

The following chronic symptoms were shown in this
group:

Case No.	Abdominal Distress	Hypogastric Distress	Epigastric Distress	Epigastric Pain
6*			X	
10*	X		X	
11*	X			X
14*		X		
17*	X		X	
20	X			
21			X	

*Allyl-bromide mixture consists of all the natural products of brom-
ination of garlic, the following derivatives probably being present:
3-bromopropene-1 (allyl bromide) 2,2 dibromopentane (bromacetel)
1,3 dibromopentane (trimethylene dibromide) 1,2 dibromopentane
(propylene bromide) 1,2,3 tribromopropane (glyceryl tribromohy-
drin).

**Chemist, 150 Woodruff Avenue, Brooklyn, N. Y.

The technic for the administration of the barium meal was exactly the same as for the roentgenographic examination of the gastrointestinal tract.

PREPARATION OF THE PATIENT FOR LAXATIVE SERIES

For the first examination, the patient presented himself in the morning with an empty stomach and without previous catharsis.

At the time of the second examination (2 days or 2 weeks later as described in the case history) the patient presented himself in the same manner, but when the barium-meal was given, the patient took a full laxative dose consisting of the following: (Each tablet contains as active ingredients) Aloin $\frac{1}{2}$ grain, Extract Cascara Sagrada 1 2-3 grains, Extract Rhubarb (Indian, not U. S. P.) 1 1-3 grains, and phenolphthalein (U.S.P.) $\frac{1}{2}$ grain.

RESULTS

Results of these tests were:

COMPARISON OF MEASURED SIZE OF STOMACH CONTENTS 6 HOURS AFTER BARIUM MEALS WITHOUT MEDICATION AND WITH LAXATIVE DOSE

Case No.	Stomach 6 Hr. Residual, With No Medication		Stomach 6 Hr. Residual, With Laxative Dose	
	Vertical Axis	Horizontal Axis	Vertical Axis	Horizontal Axis
6*	0	0	0	0
10*	3.2	14	3	10
11*	6	12	3	10
14*	1	6	1.5	9
17*	1.5	2	1.5	2
20	5	11	5	9.3
21	0	0	0	0
Average	3.3	9	2.8	8.0

*See case number in Allyl-Bromide-Mixture series.

There is a negligible difference in the amount of barium residuum found in the stomach after 6 hours when no medication is given and when a full dose of laxative is taken with the barium meal.

SUMMARY (LAXATIVE SERIES)

The average size of the stomach residuum six hours after the barium meal in five cases (with six hour retention) out of the series of seven on whom laxative tests are done showed an average of 3.3X9 cm. (vertical X horizontal axis). In repeating this test, but with a full dose of Emodin laxative, plus phenolphthalein, the average barium residuum was found to measure 2.8 cm. X 8 cm. (vertical X horizontal axis).

The small difference demonstrates the negligible effect of commonly used laxatives on the stomach contents. Analysis of the figures in this series demonstrates the remarkable consistency of the motility of the stomach when consecutive tests are made to illustrate the amount of six-hour retention.

DETAILS OF LAXATIVE STUDY

Skiagrams of 6-Hour Stomach Residues Before and After Laxatives

Note: Individual case studies with roentgenographic analysis were made with skiagrams. These studies show the barium levels of the stomach and the speed and motility of the emptying stomach, duodenum, small intestine and large intestine including the rectum. These station numbers may be added to find an index number which is given in each case for the first series (taken without laxative) and for the second series (with a full dose of laxative). The higher the index number, the greater is the motility. The difference in the index numbers represents the amount of additional motility (speed of motion of the barium meal) induced by the laxative.

Knowledge that the laxative exerted no gastragogue effect led to a consideration of substances which would exert such action. None of the common medications were found to exert direct action that would empty the stomach. Carminatives, such as garlic, are the most likely to effect this type of action. The active ingredient of garlic is stated by the literature as allyl sulfide (2-propenyl sulfide) ($\text{CH}_2:\text{CHCH}_2$) $_2$ S. There are also small amounts of allyl trisulfide (diallyl trisulfide), (C_3H_5) $_2$ S $_3$. When the active ingredients are brominated, these become allyl bromide (propene, 2,3-dibromo) (alpha-bromoallyl bromide) ($\text{CH}_2\text{Br}:\text{CHCH}_2$) or allyl bromide (3-bromopropene $\text{CH}_2:\text{CHCH}_2\text{Br}$), small amounts of allyl tribromides (1,2,3, tribromo-propene) ($\text{CH}_2\text{BrCHBrCH}_2\text{Br}$).

The vehicle for these active ingredients is the other constituents of garlic which, after bromination, consist of a protein bromide, small amounts of metallic bromide salts and inert fibrous materials (vegetable). The fate of protein bromides in digestion has been studied and it has been shown that the bromine becomes available after ingestion. The pharmacological action of the metallic salts of bromide is well known. New studies show the clinical action of the new drug as a carminative.

CHEMISTRY OF BROMINATION

When the product, Allium Sativum, is brominated in a mildly alkaline media, the following reactions take place:

1. Excess of $\text{NaOH} + \text{Br} = \text{NaBr} +$
2. Salt content $(\text{Me}) + \text{Br} = \text{MeBr} +$
3. Protein content (approx. 1% $+ \text{Br} = \text{Protein Br} +$
4. Diallyl Sulfide:

HHH HHH
C:C.C.S.C.C:C/Br²
H H H H

HHH
C:C.C Br²S
H H
+
HHH
C:C.C Br
H H

SERIES WITH ALLYL-BROMIDE MIXTURE

Sandweiss, Podolsky, Rush and Patterson⁹ have shown delayed gastric evacuation in a series of patients with duodenal ulcer. Olive oil in the usual thera-

mino acids is believed to be responsible for vomiting¹³. Duodenal hypermotility of short duration was produced in unanesthetized dogs by intravenous injection of casein digest. A long period of inhibition sometimes followed the hypermotility¹⁴.

In an effort to determine the effect of a new carminative mixture whose ingredient is Allyl-bromide, the following tests were made:

ROENTGENOGRAPHIC EXAMINATION OF THE GASTROINTESTINAL TRACT

Diagnostic points susceptible to direct examination by roentgenographic technics are first: Interference

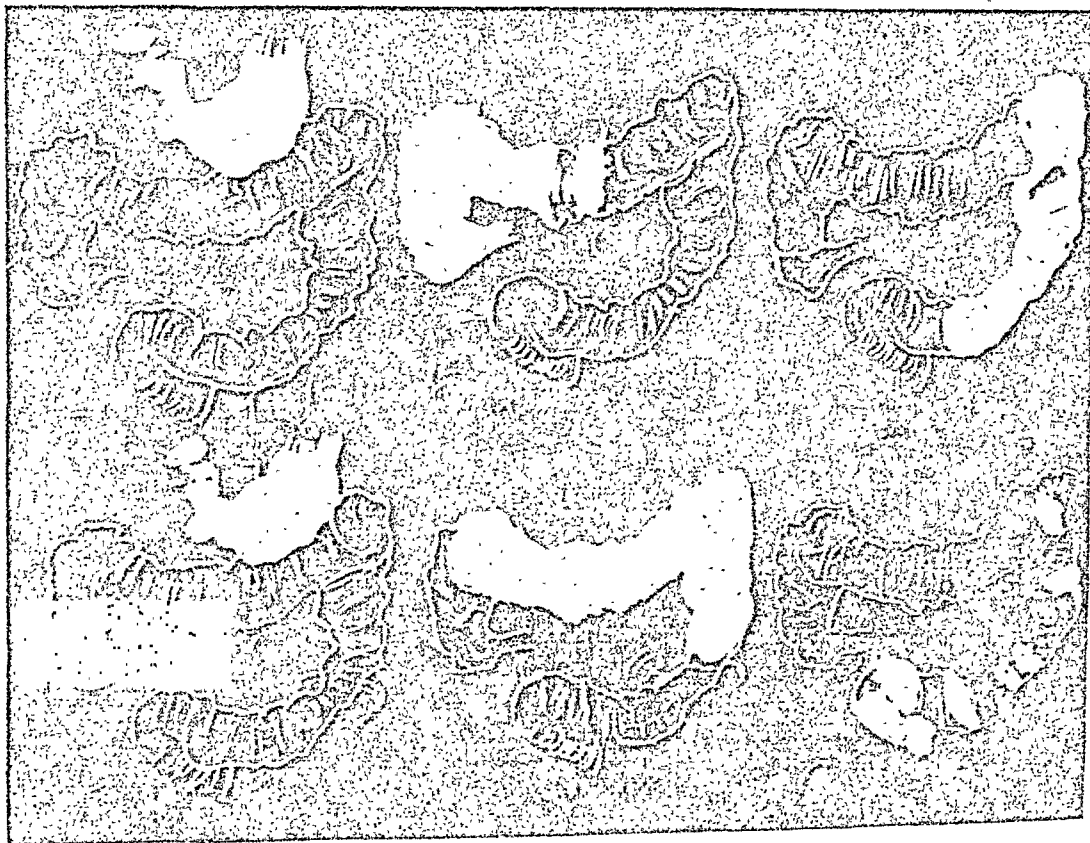


FIG. 1
AVERAGE EFFECT OF LAXATIVE

Top Row	A Immediately Following Ingestion	B 6 Hour	C 14 Hour	Lower Row	A Immediately Following Ingestion	B 6 Hour	C 14 Hour
---------	--	-------------	--------------	-----------	--	-------------	--------------

peutic doses first hastens the emptying time of the stomach slightly, but later, the formation of the fatty acids in the duodenum inhibits gastric emptying¹⁰. The emptying rate of a rat's stomach is decreased progressively as greater concentrations of glucose are fed¹¹. Five hundred to one thousand cc. of water taken with a meal had no effect on the gastric emptying time in man¹².

Intravenous administration of casein hydrolysate causes vomiting in large doses, but this vomiting is less than that caused by a mixture of ten crystalloid amino acids. The unnatural isometric formation of

with function; second, irregularities in outline, such as, filling defects, projections, niches, hour-glass deformities and spasms; third, extreme changes in position.

TECHNIC

Since the gastrointestinal tract is not directly demonstrable by roentgenographic technics, it is necessary to introduce some harmless radiopaque substance which does not interfere with function. The material employed for the purpose of examination is barium sulphate. For studying spasms of the esophagus, a thick paste which can just be swallowed is used fol-

lowing the use of a barium-water mixture. The water mixture is used first as a very narrow stricture may be present.

For the study of the stomach and gastrointestinal tract, a mixture of 120 gms. of barium sulphate with 12 ounces of water and 1/2% acacia is used.

PREPARATION OF THE PATIENT

The patient presents himself in the morning with an empty stomach and without previous catharsis. All drugs with a stimulating or inhibiting effect on the gastrointestinal tract are withheld for at least 24 hours before examination.

INTERPRETATION OF EMPTYING TIME (ACCORDING TO THE ABOVE TECHNIC)

Interpretation as outlined in the United States Army x-ray manual: Normal stomachs have been seen to empty in 2 hours. The usual emptying time is about 4 hours. Up to 6 hours is still considered to be within normal limits. Retention after 6 hours of about 1/8 or more of the ingested meal is considered distinctly pathological. The small intestine empties 6 hours after the stomach is clean. The caecum begins to fill about 4 hours after the meal and the head of barium column is at the hepatic flexure 6 hours after the meal. Barium is in the mid-portion of the transverse colon at 8 hours and the lower portion of the descending colon at 12 hours. Part should be discharged 24 hours after the meal and complete evacuation should be accomplished in about 48 hours.

DUODENAL ULCER

Duodenal ulcer, the most common ulcer formation in the gastrointestinal tract is diagnosed by consideration of the following: 1. Clinical history, 2. Emptying time of the stomach, and, 3. Direct roentgenographic demonstration of lesion.

Roentgenographic diagnosis is not concerned with the first all-important consideration. The emptying time of the stomach, when it exceeds 6 hours, must be looked upon as evidence of a distinct pathological state often associated with duodenal ulcer.

It is possible in some cases to demonstrate directly a lesion of the duodenal bulb. In other cases it is possible to demonstrate improper filling of the duodenal bulb. This is often associated with 6 hour retention.

The roentgenographic examination will, of course, emphasize certain objective diagnostic points. These objective findings, while of no greater importance than the symptomatology, have the advantage of being demonstrable. Whether or not the stomach empties is not itself of greater importance than the history and symptoms diagnostically, such as anorexia, nausea, vomiting and belching or such chronic symptoms as abdominal distress, hypogastric or epigastric distress or epigastric pain.

Direct roentgenographic evidence of disturbance of function has the advantage of being demonstrable by objective test without considering the subjective opinion of the patient as to degree of pain or discomfort.

In addition to this, certain chronic symptoms associated with slow emptying of the stomach are extremely severe and chronic.

TABLE 1

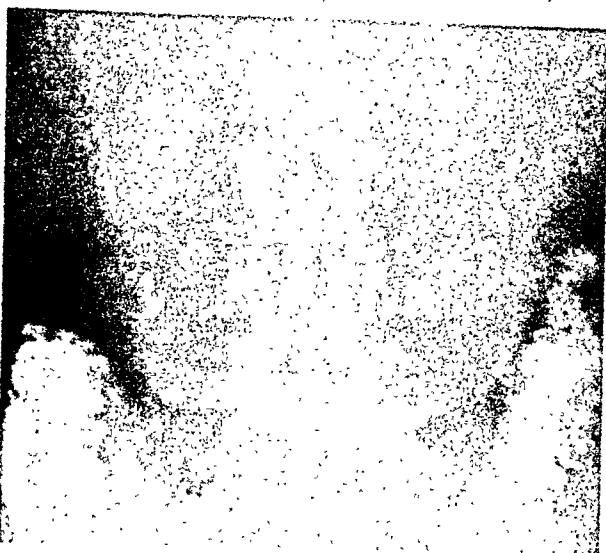
The following table compares the measured size of the stomach contents 6 hours after the barium meal without medication and the measured size of the stomach contents 6 hours after the barium meal when two 5 grain tablets of Allyl-bromide-mixture are taken with the barium meal; 2 tablets 2 hours later and 2 tablets 4 hours later.

The vertical axis and the horizontal axis of the stomach contents is measured in centimeters. These are tabulated for each of the cases of duodenal ulcer presented. The average for the cases which had 6 hour residual stomach contents with no medication was 3.6 in the vertical axis and 7.28 in the horizontal axis. The average for these same cases when given barium with the same technic but with administration of Allyl-bromide-mixture was .54 for the vertical axis and 1.21 for the horizontal axis. This is a decrease in the average from a fairly large residual at 6 hours to an almost negligible amount after the administration of medication.

TABLE 1
ALLYL-BROMIDE-MIXTURE
COMPARISON OF MEASURED SIZE OF STOMACH CONTENTS 6 HOURS AFTER BARIUM MEALS WITHOUT MEDICATION AND WITH 2 TABLETS OF ALLYL-BROMIDE-MIXTURE EVERY 2 HOURS

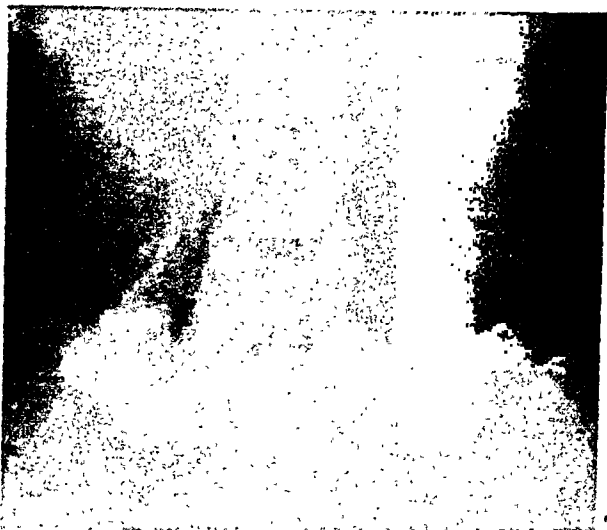
Case No.	Stomach—6 Hr. Residual, With No Medication		Stomach—6 Hr. Residual, With 3X2 Caps. Allyl-Bromide-Mixture	
	Vertical Axis	Horizontal Axis	Vertical Axis	Horizontal Axis
1	2	8	0	0
2	4	6	0	0
3	0	0	0	0
4	4	8	0	0
5	3	10	5	8
6	0	0	0	0
7	3.5	6	1.5	4
8	3	6	0	0
9	0	0	0	0
10	4	10.5	0	0
11	6	12	0	0
12	0	0	0	0
13	0	0	0	0
14	1	5	1*	5*
15	7.5	9.5	0	0
16	4.5	7.5	0	0
17	1.5	2.0	0	0
18	3.5	7.5	0	0
19	3	4	0	0
Avg.	09.5	7.28	.54	1.21

*Rugae only—No fluid level.

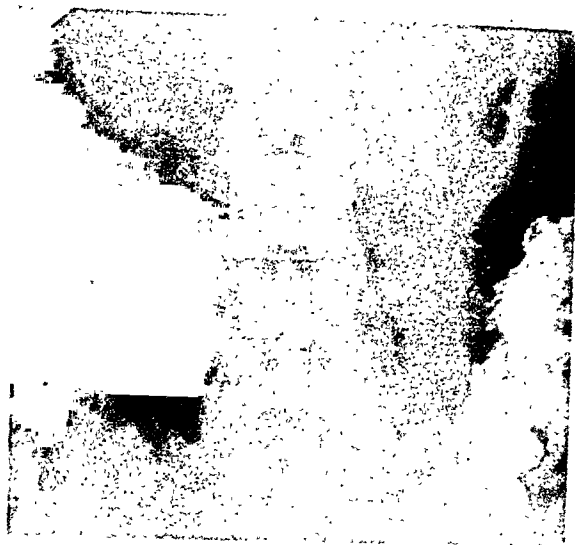


Illustrations: (Figure 2) 6 hour barium residuum shown on the same case when (1) untreated, (2) treated with laxative, and, (3) treated with Allyl-bromide-mixture.

(Figure 2) 2A Six hour residual stomach (horizontal X vertical axis) measures 11X2 centimeters.



2B. Six hour residual stomach measures 11½X4 (horizontal X vertical axis) centimeters when barium and laxative are taken together.



2C Six hour residual stomach measures 0X0 centimeters (empty) when Allyl-bromide-mixture is taken with the barium.

GASTRIC ANALYSIS OF RATS

Gastric analysis on rats receiving 25 times the human dose, given on an empty stomach (925 mgs./kilo) showed after 3 hours (cc/100 of N/10 NaOH):

	Rat No. 1	Rat No. 2	Rat No. 3	Average
Free HCL	0 cc.	0 cc.	0 cc.	0 cc.
Total Acidity	36 cc.	39 cc.	34 cc.	36.3 cc.
Combined HCL	15 cc.	14 cc.	16 cc.	15 cc.

Gastric analysis on untreated rats showed:

	Rat No. 1	Rat No. 2	Rat No. 3	Average
Free HCL	0 cc.	0 cc.	0 cc.	0 cc.
Total Acidity	12 cc.	13 cc.	11 cc.	12 cc.
Combined HCL	2.1 cc.	2 cc.	2 cc.	2.03 cc.

SUMMARY

1. This study demonstrates an agent useful in stimulating gastric motility and physiological emptying of the stomach which shows retention. The gastragogue effect was associated with subjective relief of symptoms.

2. Laxatives caused a negligible difference in the amount of barium residuum, and therefore did not increase stomach motility or secretion.

3. The animal findings show definite evidence of gastric stimulation.

REFERENCES

1. Goodman and Gilman, Pharmacological Basis of Therapeutics, Mac-Millan Company 1943, New York—Chap. 46, "Cathartics."
2. Dorland, W. A. N., American Illustrated Medical Dictionary ed. 19, Philadelphia, Saunders, 1941, p. 74.
3. Fishbein, M. (editor), Handbook of Therapy, ed. 11, Chicago, A. M. A., 1937, p. 31.
4. Gould, G. M., Gould's Medical Dictionary (Scott, R. J. E., editor) ed. 3, Philadelphia, Blakiston, 1934, p. 54.
5. Hare, H. A., Text-Book of Practical Therapeutics, ed. 21 Philadelphia, Lea & Febiger, 1930, p. 90.
6. Marcovici, E. E., Garlic Therapy in Diseases of Digestive Tract based on 25 years' experience, M. Rec. 153-65, 1941.
7. Potter, S. O. L., Therapeutics, Materia Medica and Pharmacy, ed. 15 (revised by R. J. E. Scott), Philadelphia, Blakiston, 1931, p. 118.
8. Solis-Cohen, S. & Githerns, T. S., Pharmacotherapeutics, Materia Medica and Drug Action, New York, Appleton, 1928, p. 1021.
9. Federation Proceedings, Vol. 3, p. 40, 1944.
10. Apperly, F. L., Gastroenterology, Vol. 1, p. 1127-32, 1943.
11. Fenton, P. F., and Pierce, H. B., Federation Proceedings, Vol. 3, p. 57, 1944.
12. Van Lier, E. J., and Northup, D. S., Gastroenterology, Vol. 2, p. 195-200, 1944.
13. Cox, S. M., and Mueller, A. J., Federation Proceedings, Vol. 3, p. 56, 1944.
14. Robinson, H. W., and Oppenheimer, M. J., Federation Proceedings, Vol. 3, p. 39, 1944.

Anal Fissure

By

DAVID C. DITMORE, M. D.*
BOSTON, MASSACHUSETTS

AN ANAL FISSURE is a benign crack or ulcer at the anal margin or in the anal canal, and is to be distinguished from an acute abrasion which heals after an acute course with or without treatment.

Although chronic anal fissure has not been produced experimentally, the cause can be found, it seems to me, in the pathology involved and in the anatomic structure in and about the anal canal. There is, first of all, slight trauma with inflammation of the tissue and a consequent loss of elasticity. As a result, splits or abrasions occur into which infection enters, and consequently there is an extension of the inflammatory process, with further loss of elasticity. In the early stages, at least, nature makes an attempt at healing, but because the sphincter muscle of the anus is contracted, the sides of the split are in apposition and heal by first intention with a narrow band of scar tissue. Subsequently, during a period of stress produced by straining at stool, or in fact, any body exertion, a second crack or cracks occur. These cracks may be in immediate apposition to and parallel with the original scar, or they may be at an angle to it. This phenomenon influences the type of lesion which develops and has a distinct bearing upon treatment. Parallel breaks result in long, simple cracks with a smooth base. Crisscross or diagonal breaks result in an irregular, rounded, typical ulcer with trabeculated and pitted base. Cracks usually are much deeper than ulcers and may bleed more freely. The depth of any fissure depends, therefore, upon the type of lesion and degree and extent of inflammation. It depends also upon its location in the anal canal, ulcer characteristics predominating as the pectinate line is approached.

Buie, of the Mayo Clinic, has shown that there is more supporting tissue on each side, less anterior and least of all posterior to the anal canal, and this lack of support agrees exactly with the occurrence of fissure. It occurs most frequently posterior, rarely anterior, and almost never on the sides of the canal.

CLASSIFICATION

Fissures can be classified, according to their location, as marginal, interanal and ano-rectal. The marginal fissure may be seen upon inspection or by simply spreading gently the external anal opening. The interanal fissure is demonstrated with the patient anesthetized and the walls of the canal spread apart with the fingers or a speculum. The ano-rectal fis-

sure involves the pectinate line; usually has the characteristics of an ulcer, and is not seen until the patient is under anesthesia. At that time a speculum is inserted and the ulcer brought clearly into view. Not infrequently the circular fibers of the sphincter muscle may be seen forming the ulcer base.

SYMPTOMS

The subjective symptoms of all fissures are more or less uniform, varying only in frequency of attack and intensity of discomfort. The patient complains of intermittent traces of blood, pain and (in many cases) itching. The blood is of significance only as an aid in diagnosis. It appears usually as a stain on the toilet paper. Pain is characterized by burning and smarting at or following defecation. Less frequently it may be cutting, piercing, aching, steady or throbbing.

The intensity and duration of discomfort varies tremendously, depending apparently upon individual susceptibility to pain and the presence of infection. One patient will complain only of slight uneasiness during the passage of fecal material, while another, with an identical lesion will be completely demoralized because of the severe and continual agony. Very often the patient complains of a sensation of tightness and frequent stools, but inability to completely empty the bowel.

Objective symptoms are few and will be discussed under the next paragraph dealing with examination.

EXAMINATION

Every precaution must be taken to gain the patient's confidence before the examination begins, and subsequently nothing should be done to disturb that confidence.

After placing the individual in position for examination, assurance is given that there will be no discomfort. Very gently then the buttocks are spread apart and the area inspected. A small, firm skin tag projecting from the anal margin deserves particular attention, because at its base or on its ventral surface a fissure may be immediately visualized. When no pathology is seen the margins of the anus are gently separated and in a certain percentage of cases a fissure will appear. In the majority of cases, however, inspection fails to disclose information of significance.

Palpation with the gloved and well-lubricated index finger of the right hand is by far the most important step in the search for fissure. Pressure is first exerted on the sphincter ring. If a fissure is manipulated the patient will complain of pain. When no discomfort is produced insertion of the finger into the anal canal is begun. Every few millimeters pressure

*Instructor, Dept. of Proctology, Boston University School of Medicine.
Proctologist—Carney Hospital, Corey Hill Hospital.
Consulting Proctologist—Brooks Hospital.
Read before New England Society of Physical Medicine, Boston,
March 22, 1944.
Submitted June 30, 1946.

is exerted, first in one quadrant, then in another. The instant a tender point is compressed the patient will register discomfort, and in the absence of any other proved lesion a presumptive diagnosis of fissure is justified. Usually the thickened edge and base of an ulcer is felt. The necessity for further examination must then be considered, but so far as fissure is concerned there is no need to cause the patient unnecessary discomfort. At the time of examination, in addition to making the diagnosis of fissure, it is also necessary to note the condition of the anal sphincter. Is it spastic, contracted, patulous, competent or incompetent? Treatment of the fissure is based upon all conditions present.

DIFFERENTIAL DIAGNOSIS.

In any patient complaining of chronic anal pain at or immediately following defecation, the presence of fissure must be strongly considered until examination shows other pathology. Conditions which must be considered in making the diagnosis are in order of frequency of appearance: Uncomplicated internal hemorrhoids, internal thrombosed hemorrhoids, fistula-in-ano, abscess, coccygodynia, tumor involving the pectinate line, and cryptitis.

Gonorrhea, various fungus infections, and other diseases may, of course, occur in and about the anal canal, but are of such rare occurrence that they are of no great importance in the practice of the average proctologist.

Strange as it may seem the diagnosis of internal hemorrhoids is most frequently confused with that of fissure, although the symptoms are so diverse that doubt should rarely exist. Uncomplicated internal hemorrhoids cause little if any discomfort, but may bleed freely. Fissure is almost always accompanied by intermittent or constant pain, and bleeding is evidenced usually only on clothing or toilet paper. Internal thrombosed hemorrhoids are characterized by an acute onset, rapid course, severe discomfort, and a painful lump which is palpable to the examining finger. Fistula and acute abscess which presents external to the sphincter muscle are readily diagnosed. When above the sphincter muscle there is usually a history of acute onset, visible pus, or a palpable tumor, elevated temperature, leukocytosis, and general malaise. If the pectinate line is involved there is in addition to these symptoms, steady intractable pain, not particularly associated with defecation. Fissure is mistaken for coccygodynia more frequently than vice versa, and indeed the symptoms are so similar that such an error is not always to be criticized. In either condition the patient may complain of pain on reaching, sneezing, coughing or straining in the act of lying down, getting up, and at defecation. However, with fissure the pain is likely to be definitely localized in the anal canal, whereas in coccygodynia localization is not exact, but is placed anywhere between the end of the spine and the anus. Also the pain of fissure is caused by passage of an irritating stool, rather than the act of straining. Like-

wise, digital examination in cases of fissure may be so painful as to be impossible, whereas in coccygodynia it does not increase the discomfort. Again, the sphincter muscle in fissure is usually spastic or contracted, while in coccygodynia it is normal.

New growths, accompanied by pain, are usually to be distinguished from fissure by palpation, the excruciating steady discomfort, and the fact that pain is not necessarily initiated by defecation but is aggravated thereby. In cases of malignant, tuberculous or syphilitic ulcer, gonorrhea, the fungi and other rare conditions, diagnosis may depend upon microscopic examination. In cases of malignant, tuberculous or syphilitic ulcer, diagnosis may depend upon a microscopic examination. Symptoms of true Cryptitis occur rarely, pain is sharp and of short duration, and not so regularly aggravated by bowel movement. Non-specific inflammation originating proximal to the mouth of a crypt or crypts, and involving them only secondarily, is probably the first stage of fissure.

A type of fissure almost always overlooked is that in which pain is evidenced during micturition or upon intercourse, particularly at the time of ejaculation. This occurs in the male, and may be so severe as to cause prostration or even loss of consciousness. Therefore any male patient with this history, in the absence of positive urological background and findings, should be investigated by the proctologist.

TREATMENT

Many methods of treatment have been suggested. One is the injection of a long-lasting anesthetic in oil beneath the fissure. Relaxation of the sphincter in the area of the lesion as a result does at times permit healing, but in those cases which we have seen, the lesion and pain return in the matter of two or three weeks or a few months.

The oldest and most thoroughly discredited method of treatment is cauterization of the fissure with silver nitrate stick. We have never seen a cure result, but do see many patients absolutely demoralized because of the increase in discomfort during and following the procedure.

Gant claims excellent results from splitting the fissure with the scalpel and extending the incision posteriorly through the fibers of the external and internal sphincters. The wound is painful and takes approximately three weeks to heal.

Fissurectomy, together with moderate dilation, as advised by Buie, is a method of treatment which gives a high percentage of cures. This operation consists, in addition to dilation, of excising the fissure and any accompanying pathology by means of a V-shaped incision extending down to the fibers of the external sphincter muscle, and then suturing the cut edges of the mucous membrane to the pectinate line. Swinton favors a similar procedure but in addition makes a simple longitudinal incision in the posterior midline, severing a portion of the fibers of the sphincter

muscle. The advantage of this operation is that it is not necessary to select cases, and that cure is obtained. The disadvantages are that postoperative pain is severe and convalescence prolonged.

Simple dilation of the sphincter muscle followed by adequate treatment is, in my experiences, the method of choice in selected cases. The advantages of this operation are that cure may be expected, pain is immediately controlled, and the patient resumes his normal activity on the fourth or fifth day.

Many variables must be considered in deciding whether or not dilation alone or dilation with some surgical procedure is to be carried out, and the surgeon's decision is of great importance to the patient, since it determines whether he will experience considerable pain and a relatively prolonged convalescence, or if he will be immediately relieved of discomfort and be able to resume his work within three to five days. There are three conditions which must be present if dilation alone is to be considered. In the first place the fissure should be relatively small, the base should be smooth and there should be a minimum of scar or any other inelastic tissue. Such inelastic fibers, whether of the lining of the anal canal or of the subcutaneous sphincter muscle, must be severed. Also, the anal sphincter must be spastic or contracted. Very often this can be determined at the time of examination. In some cases, however, spasticity or contraction is evidenced only after the anal ring is dilated up to two and a half to three centimeters, or more, under anesthesia. It follows, therefore, that decision as to just what is to be done cannot be determined until the operation is in progress. Again, it is necessary for the pelvic outlet to be large enough in some one direction to admit the fingers for dilation. We have found that when the distance between the ischial tuberosities or the distance between the tip of the coccyx and the symphysis pubis is seven centimeters or more, dilation alone can be considered.

OPERATION

When the patient is relaxed, the index finger of the right hand is first inserted through the anal sphincter and pressure exerted in every direction until two fingers can be introduced. The index finger of the left hand is then inserted on top of the index finger of the right hand. These two fingers are then manipulated until no further relaxation can be obtained. As dilation proceeds more fingers are then added until the procedure is completed. The tissues are easily torn by a too enthusiastic operator, lack of elasticity of the mucous membrane, or because of poor anesthesia. There should be no turning or twisting of the fingers at any time. They should be inserted directly and should be withdrawn without a rotary movement. Otherwise, tears and abrasions will take place.

Much experience is required before consistently good results are obtained from this method of treatment. Overdilation, with the resulting incontinence, is very

unlikely to occur if we remember that women over forty, particularly if they have had perineal tears, do not need as much dilation as younger people, and that as age increases, less and less dilation is necessary. Individuals over seventy years of age should rarely be dilated more than two fingers. Poorly nourished individuals—young or old—do not need radical dilations.

ANESTHESIA

Relaxation essentially without danger of complication is best obtained with caudal and parasacral anesthesia. Complications such as nausea and headache are rare. The patient is able to move to or from the operating table, and to turn as desired in bed as soon as he returns to his room. Within one or two hours he can be propped up in order to read or to be more comfortable.

POST OPERATIVE CARE

After dilation, a mild, nonirritating antiseptic seems to be of definite value, particularly in cases where tears have occurred. Complications are avoided by means of a pressure dressing applied for thirty-six hours. We have found that morphine gr. 1-6 and scopolamine gr. 1-150, given subcutaneously just after operation, help to prevent prolonged nausea. They serve also to quiet the patient and to allay any discomfort. Scopolamine is never repeated and morphine only in rare instances. Fluids are given orally as soon as they can be retained, and a liquid diet ordered for the first day. On the second day the patient goes on general tray, is given a mild laxative the second night, and has a painless movement on the morning of the third day. That afternoon he is discharged from the hospital. Subsequently, he is seen frequently at the office, where internal hemorrhoids are treated, and every precaution taken to assure healing.

SUMMARY

A working classification of anal fissure is suggested. Familiarity with the fact that only a small proportion of fissures are visible upon inspection of the external anal margin and that chronic pain indicates the presence of this lesion in a very high percentage of cases will enable us to make the correct diagnosis much more frequently than is done at present. A sphincter muscle so contracted or spastic that digital examination causes severe distress is almost diagnostic. Uncomplicated internal hemorrhoids are not painful and digital examination does not cause distress. Diagnosis of fissure depends largely upon history or palpation. In expert hands an inter-anal or ano-rectal fissure may often be visualized through the anoscope or sigmoidoscope, but in the presence of an acute lesion such an examination is best postponed until the patient is anesthetized. Coccygodynia is the only condition which presents almost unsurmountable difficulties in differential diagnosis. Not infrequently both fissure and coccygodynia are pres-

ent at the same time, and the cure of the fissure followed by a proper cushion results in a comparatively happy patient.

CONCLUSIONS

Our records show that in properly selected cases cure of anal fissure by dilation may be expected. Clinically, the resulting healed scar is just as wide if not as deep as that following excision. At the present time we are abstracting some six or eight thousand

case histories, and statistics from them will be published at a later date. There is no doubt, however, that a substantial majority of anal fissure can be cured in this way, and it does not seem fair to the individual patient to subject him to the painful and expensive experience of the cutting operation when dilation alone or with some slight modification gives such a high percentage of cures. Pain and disability is in direct proportion to the amount of cutting necessary.

Editorial

POSITIONING IN THE ROENTGENOLOGICAL EXAMINATION OF THE STOMACH

It is a well-known fact that the roentgenological examination of the stomach is tied up with the many difficulties in presenting a three-dimensional organ on a two-dimensional film. No thorough roentgenological examination can be done without having films taken at different angles, in different positions, and at different stages of filling. A certain routine has developed in having most of the roentgenograms of the stomach taken while the patient is lying on his stomach or standing up. These are the two basic positions under which the examination is performed. Besides the above mentioned ones, oblique positions are often added.

Recently, Albert Oppenheimer, who has frequently contributed to the literature on the roentgenological examination of the gastro-intestinal tract, has published a very interesting study. He emphasizes that his method is only an additional one, and should be used only in conjunction with routine examinations. Oppenheimer draws our attention to the roentgenological examination in supine position of the patient. This technic gives more detail of the pathology of the corpus and rear wall of the stomach, which he illustrated by very interesting case reports. As suggested, he has combined films taken during routine examination with films taken while the patient is in supine and supine-oblique position. He uses the routine contrast substance.

Among his findings are ulcers of the rear wall of the stomach. In looking over his roentgenograms, it is astonishing to see what large niches cannot be detected during the routine examination, however, are well demonstrated by this method. Ulcers and carcinomas in the region of the cardia are especially well discernible, and some are detectable only by this po-

sitioning. The supine position, of course, is well known for the visualization of minor diaphragmatic hernias. Films in supine position are different in appearance from the routine views, and it is important for the diagnostician to familiarize himself with the normal outline of the stomach and its mucosal pattern in this aspect.

The roentgenological examination of the stomach would be too complicated if we used all these methods in every case. It would make the examination too prolonged and too expensive. We have to view Oppenheimer's suggestions as an additional technic for more thorough studies, according to the need. These facts emphasize that the roentgenological examination of the GI tract should not be left to the technical staff of an office or X-ray department, but that it has to be closely supervised by an experienced physician. Only the experienced eye can evaluate the findings, and insist that, besides the routine technic, additional, rarely used methods help to clarify the diagnosis. I am pretty sure that even in the experienced hands of Oppenheimer, only a few films taken in supine position, showed pathology. It would be roentgenologically a waste if this method as brought again to our attention by Oppenheimer, would be added to every roentgenological examination. I think this is Oppenheimer's idea also. However, it is always well to scrutinize our methods and check that they have not deteriorated by too much office routine. In this sense it is good that we are reminded once in a while by an expert, of the importance of diversity in the methods of examination.

—Franz J. Lust.

REFERENCE

- Oppenheimer, Albert. The Supine Projection in the Diagnosis of Lesions of the Corpus and the Posterior Wall of the Stomach. *A. Journal of Roentg. and Radium Therapy* 55,4,454-463. April, 46.

Book Reviews

Manual of Applied Nutrition. The Johns Hopkins Hospital (send \$1.50 to Student Dietitian's Fund, the Johns Hopkins Hospital, Baltimore, 5, Md.)

The manual has been compiled by the dietary staff under the direction of the Committee on Nutrition of the Johns Hopkins Hospital, is of value to doctors, nurses, dietitians and medical students, and carries a foreword by E. V. McCollum. Very little of the book pertains to the particular routine of their hospital, but is rather of general interest. The description of diabetic diet is extremely brief. One wonders how hypertrophic arthritis can be symptomatically improved without a low-carbohydrate diet. The book is naturally not concerned extensively with the methods of preparing specific diets but is rather a tabulation of how to proceed once the diagnosis is complete.

Allergy (2nd Edition). By Ulrich Urbach, M. D., and Philip M. Gottlieb, M. D., Pp. 968 (\$12.00), Grune and Stratton, Inc., New York, N. Y., 1946.

One must admire any monumental work such as "Allergy." Probably one of the most complete texts on a subject of increasing interest, the 2nd edition has added new material and brought its references completely up to the minute. Among the new material is a section on the psychosomatic aspects of allergy which, proportionate to the size of the book, does fair justice to the studies which have been reported by investigators in this field. The book is concisely written, beautifully printed and illustrated and is so exhaustive and practical in its coverage and mode of attack, that no question concerning allergy is omitted and the practitioner will find it a liberal education. Food allergy and allergic diseases of the digestive tract are covered with proportionate thoroughness.

Medical Biochemistry (2nd Edition). Mark R. Everett, Ph.D., Pp. 767 (\$7.00), Paul B. Hoeber, Inc., New York, 1946.

This is an exhaustive, practical text, brought up to date so as to include amino-acid therapy, cephalin

fractions, the Rh factor, and thiouracil, with new tabulations on antibiotic substances, bacterial polysaccharide haptens and turnover numbers of enzymes. Each chapter is divided into three principal sections, dealing with chemistry, metabolism and pathology, so that the pathology sections can be omitted during the basic course without fear of confusion. The book, which is well-written and very readable, is recommended for medical students and also for physicians who desire a clear, concise text for reference or review.

The Management of Obesity. Louis Perner, M. D., Pp. 144, Personal Diet Service, Publishers, New York, \$3.00 Postpaid.

Perner has handled his subject very well and produced a book that should be of value to the busy general practitioner. Like most authors on this subject, he regards overeating as the commonest cause of obesity and wisely stresses the importance of the psychological investigation to determine the cause of abnormal appetite. Endocrine obesity is well described and it is refreshing to find an author who regards the endocrine treatment of obesity as useless except in the case of hypothyroidism. Chief attention is devoted to diet therapy and a few valuable exercises are described.

Diabetic Care in Pictures. Helen Rosenthal, B. S., Frances Stern, M.A., and Joseph Rosenthal, M.C., Pp. 150 (\$2.00), J. B. Lippincott Co., Philadelphia, 1946.

This is an attractive, sturdily bound volume dealing with the practical phases of diabetes mellitus in pictures, charts, graphs and simple prose. Apparently nothing is omitted which would be useful to the intelligent patient. Calculation of diets, selection of weighed amounts, the use of the various insulins, care of syringes and the control of weight, as well as precautions in emergencies—all are graphically described and this book may be the most desirable yet to appear for the patient himself to own and read.

Abstracts of Current Literature

(Microfilm copies of papers may be obtained from the Medicofilm Service of the Army Medical Library at 25c per each complete article, not exceeding 25 pages in length—and 10c for each additional 10 pages or fraction thereof. Prepayment is not requested. Remittances may be made with subsequent orders and in such manner as found most convenient. Address—Medicofilm Service, Army Medical Library, Washington, D. C.)

M. K. F. FRIEDMAN, Associate Editor in Charge of Abstracts, Philadelphia, Pa.

*D. J. ABOLOFIA
B. R. ADOLPH, JR.
HELEN BATTLE
*WM. D. BEAMER
IVAN BENNETT
*J. EDWARD BERK
J. B. BERNSTINE
G. P. BLUNDELL

*With the Armed Forces.

R. L. BURDICK
R. E. CAPPS
*F. X. CHOCKLEY
*C. G. CLEMENTS
*JOHN J. COX
H. W. DAVENPORT
E. R. FEATHER
CARMELA FORDERARO
*S. A. FRIEDMAN
J. LOGAN IRVIN

G. KLENNER
*EDGAR G. KNERR, JR.
S. A. KOMAROV
HARRY METZGER
M. J. OPPENHEIMER
K. E. PASCHKIS
*I. J. PINCUS
B. C. RIGGS
F. E. ST. GEORGE
*FREDERICK H. SCHARLES

N. M. SMALL
G. N. N. SMITH
WM. J. SNAPE
G. W. STAVRAKY
HORACE STILYUNG
I. M. THEONE
*C. A. H. TICE
ADOLPH A. WALKLING
D. A. WOCKER

CLINICAL MEDICINE

HULE, V.: *A new sign in the blood picture during typhoid fever.* (*Lekarske Listy*, vol. 1, No. 12, pp. 273-277, 1946.)

In 52 cases of typhoid fever histiocytes were found in the peripheral blood. This phenomenon was observed in all patients with E. typhosa infection but also in bacterial endocarditis. The histiocytes are large cells, mostly of endothelial origin, and are not numerous. They appear in the blood before the agglutination tests become positive. O. Felsenfeld.

STOMACH

WILEY, H. M.: *Etiology and treatment of heartburn of pregnancy.* (*Amer. J. Obstet. Gynecol.* v. 51, p. 221, 1946.)

The basis of the heartburn of pregnancy is not an organic lesion but a functional disturbance of gastric physiology due to the shift in the anatomic position of the stomach produced by the expanding uterus. Forcing of the greater curvature towards the cardia doubles the gastric emptying time and results in reverse peristalsis. In addition, as pregnancy progresses there is atony of the cardiac sphincter. The acid gastric contents acting on the esophagus results in the burning sensation which is referred to the heart region.

Prostigmine by mouth was tried in 20 pregnant women complaining of heartburn. Relief was complete in 15 cases and partial in 2 cases. Increased gastric peristalsis and emptying rate were believed to be responsible for the relief. Side reactions were minimal. Prostigmine had no effect on the pregnancy.

— J. B. Bernstine.

GRAVES, GAYLORD W.: *Borderline cases of pyloric stenosis.* (*Arch Pediat.*, v. 63, p. 112, March, 1946.)

Since often in particular instances it seems reasonable to evaluate uncertain conditions, it is worth while to review the behavior of typical borderline pyloric stenosis cases under non-surgical supervision. This is not to be construed as detracting from surgical management when the diagnosis is definite as it is in the face of projectile vomiting and weight loss. A child under 2 years of age with visible peristalsis and projectile vomiting for a period of even only 48 hours probably has pyloric stenosis. If constipation and a

palpable tumor are present operation should be deferred only long enough to restore fluid and salt balance. X-ray is of little aid in this condition. When a child has inconstantly projectile vomiting for a few days only and visible peristalsis without constipation or palpable tumor, the diagnosis of pyloric stenosis is unwarranted without further observation. When presented with such a case one should restore fluid balance, give gastric lavage, and withhold attempts to feed for 6-12 hours. Then one should institute thickened cereal feedings combined with atropine, gr. 1-500. The thick cereal feeding should be limited to 1 oz. and the water to 1 oz. every 4 hours. Sugar content of the diet should be low and synthetic vitamins substituted for the natural. — Wm. J. Snape.

BOWEL

W. T. COOKE ET AL.: *Anomalies of the intestinal absorption of fat. 1. Determination and significance of fecal fat.* (*Quart. J. Med.*, v. 15, p. 141, April, 1946.)

The authors introduced a diet containing fat 50 gm. carbohydrate 250 gm., and protein 75 gm. to 15 cases of diarrhea, 12 cases of varying types of anemia and 79 others in which fecal fat would be expected in excess. After 48 hours of such diet, the stools were marked and collected for two to four days. These stools were then analyzed for neutral fat, fatty acids and soap. The percentage absorption was then calculated as the difference in the intake and the amount excreted. While aware of the normal excretion of non-dietary fat, this was disregarded in this series. It was found that cases with a percentage absorption of less than 85 invariably showed signs or symptoms confirming the presence of a fat absorption defect. Further evidence was gained that the percentage hydrolysis of fat in the feces has little significance in regard to pancreatic function. The amount of soap in the feces also seemed to bear no clinical relationship. Thirty-five cases with a proved fat absorption defect were investigated radiographically, and showed "deficiency patterns" or evident slowing, while in cases of diarrhea where charcoal passed through the entire tract, the fat absorption was normal. In some of the cases of defective fat absorption, although 70 to 80 percent absorption had occurred, there was little or no change in the blood fat. — W. D. Beamer.

PANCREAS

DE CASTRO BARBOSA, J. J., DOCKERTY, M. B., AND WAUGH, J. M.: *Pancreatic heterotopia: Review of literature and report of 41 authenticated surgical cases.* (*Surg. Gynecol. Obstet.*, v. 82, p. 527, 1946.)

Aberrant pancreatic tissue is usually detected in the fourth to sixth decade, and is more often found in the male. Hypoglycemia or hyperinsulinism is frequently found. Patients suspected of having a pancreatic tumor because of hyperinsulinism should be subjected to search for aberrant pancreatic tissue if no such tumor is found in the pancreas at operation. Stomach, duodenum and jejunum are the more usual sites of aberrant pancreatic tissues. Adjacent tissues may show distinct pathologic change, such as fat necrosis, necrosis, hemorrhage and ulceration. In 25 of the 41 surgical cases of pancreatic heterotopia reported the aberrant pancreatic tissue was responsible for conditions of clinical significance. — Wm. J. Snape.

LIVER AND GALL BLADDER

SCHIFF, L.: *Hepatitis.* (*Cincinnati J. Med.*, v. 27, p. 97, 1946.)

Special attention has been focussed on various types of hepatitis because of the increased incidence during the war years. In combat areas the infectious hepatitis was a severe problem; in some staging areas hepatitis following vaccination for yellow fever was also a problem of great importance. Finally the increase in the use of arsenicals in venereal disease therapy resulted in a greater number of arsenotherapy hepatitis.

Infectious hepatitis and homologous serum hepatitis have a great deal in common except that in the latter the fever is less marked, and the incubation period 60 to 120 days rather than 18 to 30 days. Necrosis and autolysis of the liver cells, diminution in the size of the lobules and their invasion by leukocytes and histiocytes are the main pathological findings. In the infectious and homologous serum hepatitis liver damage can be shown by liver function tests to be present before the onset of jaundice. In arsenotherapy hepatitis, a sudden fever, anorexia and vomiting, together (but not always) with a rash may mark the disease before the advent of jaundice.

Treatment is by bed-rest, and by high protein and high carbohydrate diets. In infectious hepatitis gamma globulin given during the infectious stage is helpful. Psycho-therapy in cases mentally depressed by their long confinement to bed is advised. — B. R. Adolph, Jr.

SPAIN, D. M.: *Portal cirrhosis of the liver. Review of 250 necropsies with reference to sex differences.* (*Am. J. Clin. Pathol.*, v. 15, p. 215, 1945.)

In the series presented there were only 60 females as compared with 190 males. At death the average ages were 48.6 years for women and 56.3 years for men. Chronic alcoholism was shown in the history

of nearly all cases. Women died from the cirrhosis more frequently than the men; they also showed a higher incidence of jaundice and ascites. Esophageal varices were more predominant in incidence in the men. — N. M. Small.

GOLDSMITH, G. A.: *Nutrition and Cirrhosis of the liver.* (*Intern.*, v. 12, p. 401, June, 1946.)

In this brief review it is indicated that inadequate supply of certain nutritive materials results in extensive pathologic changes of the liver, including fatty infiltration, necrosis and cirrhosis.

Experimental work has shown that low protein diets result in liver hemorrhage and necrosis. Continued low protein or high fat diets lead to extensive fibrosis and atrophic cirrhosis. High protein diets, methionine, or choline and cystine prevent these damaging changes in the liver. Dietary deficiency in vitamin B complex results in fatty livers; the responsible fraction of the B complex is inositol.

Treatment of liver disease in man by high protein diet, with due attention to the quality of the protein, is preferred to high carbohydrate diet. Probably the protein-sparing action of carbohydrates accounts for the beneficial effects of the high carbohydrate diets in vogue in the past. Fat-soluble vitamins A and K, stored in the liver, are lacking in livers which are injured and should be included in the diet. Prothrombin deficiency may be due to vitamin K deficiency and must be determined by blood coagulation. Menadiol should be given. The vitamin B complex and other lipotropic substances, such as choline and methionine, in large amounts, together with a high protein, high carbohydrate and low fat diet have proved successful in the treatment of liver cirrhosis and toxic and infectious hepatitis. — H. Stilyung.

ZASTOW, J., COUNSELLER, V. S., HEILMAN, F. R.: *The excretion and concentration of penicillin and streptomycin in the abnormal human biliary tract: Preliminary report.* (*Proc. Staff Meet., Mayo Clinic*, v. 21, p. 94, Feb. 20, 1946.)

Studies on the excretion and concentration of penicillin and streptomycin in diseased states of the human gallbladder and bile ducts revealed neither antibiotic in the gall bladder when the cystic duct was obstructed by a stone. Once the antibiotics entered the gall bladder in cases in which the cystic duct was patent, they remained there for long periods. However, there was no indication that they were either concentrated or absorbed through the wall of the gall bladder. Studies on patients with a T tube in the common duct revealed that the antibiotic agents were excreted in high concentration in the hepatic bile of patients who had normal livers; that penicillin was concentrated by the liver before excretion into the bile, and that streptomycin was not concentrated. In cases of obstructive jaundice the ability of the liver to excrete the antibiotics was impaired; the impair-

ment was increased with the degree of hepatic damage. From these studies it was concluded that obstruction must be removed and free drainage established before the antibiotic agents can be expected to overcome an infecting organism in the biliary tract.

—E. Tallant.

ULCER

TRYB, R.: *Callus ulcer of the greater curvature of the stomach.* (*Lekarske Listy*, vol. 1, No. 12, pp. 277-279, 1946.)

The description of a relatively rare, benign chronic gastric ulcer of the greater curvature, is described. The patient, a young woman, was cured by partial gastrectomy.

—O. Felsenfeld.

COX, T. J., AND JUNNILA, O. B.: *Relationship between anxiety neurosis and duodenal ulcer.* (*Calif. West. Med.*, v. 64, p. 240, 1946.)

Study of a series of 161 patients with a history of anxiety neurosis revealed that 50 percent had duodenal ulcers (X-ray findings) before hospital admission and the remainder were found to have ulcers when given careful examination. Radiologic evidence of a lesion was usually found only after the onset of the anxiety state. Psychotherapy and dietary measures brought about great improvement. While not all patients with anxiety neurosis show evidence of duodenal ulcer, probably all patients with duodenal ulcer do have a history of anxiety or emotional instability. The role of the autonomic nervous system and its central stations in regulating gastrointestinal functions is emphasized.

—G. Klenner.

GRIMSON, K. S., TAYLOR, H. M., TRENT, J. C., WILSON, D. A., & HILL, H. C.: *Effect of thoracic vagotomy on functions of stomach of patients with peptic ulcer.* (*Southern Med. J.*, v. 39, p. 460, June, 1946.)

Ulcer symptoms were exhibited by 25 patients for periods varying from 3 to 35 years. All cases were refractory to medical management. The youngest patient at time of operation was 27 years old, the oldest 62 years. About 10 centimeters of each vagus trunk was resected within the chest and the esophageal nerve plexus excised. Because of retention or obstruction, gastrojejunostomy or pyloroplasty was also performed in 5 of the 25 patients who were vagotomized. Four to 18 months after operation the patients showed no evidence of either ulcer or recurrence of ulcer. Ulcer pain was absent in all cases. Gastric motility and secretion were depressed in the fasting state. Apparently not only the psychic or reflex mechanism but also the chemical mechanism of gastric secretion is altered. The authors suggest that pyloroplasty or gastrojejunostomy be combined with bilateral vagotomy to give maximum benefits in certain cases, particularly in the presence of obstruction.

—M. H. F. Friedman.

MUSICK, V. H., HOPPS, H. C., AVEY, H. T., AND HELLBAUM, A. A.: *The effect of caffeine on gastric secretion.* (*South. Med. J.*, v. 39, p. 651, Aug., 1946.)

The gastric secretory response to caffeine using the Ivy caffeine gastric test meal was determined on 39 individuals, ten of whom were considered free of gastric disease, twenty-five having active duodenal ulcer, and four with gastric ulcer in the active phase. Fifteen of the duodenal ulcer cases exhibited a persistently high secretory response without tendency to return to the basal level for two hours. A similar response was noted in two of the gastric ulcer cases. In the normal cases, there was a marked drop in secretion during the second hour of the secretory phase. The degree of gastric hypersecretion in response to caffeine tends to indicate the activity of the disease.

—G. Klenner.

SURGERY

BLACK, B. M., AND EVERT, J. A.: *Nomenclature of certain gastric operations.* (*Proceed. Staff Meet, Mayo Clinic*, v. 21, p. 229, June, 1946.)

Designation of a particular operation by a given person's name is inadequate, but frequently other methods of terminology are awkward. Descriptive terms are necessary but the terminology should have a specific, restricted and unvarying meaning. The surgeon's name attributed to an operation does not always mean that he was the originator of the technique. Gastro-duodenal anastomosis or Billroth I operation has had many modifications, mainly attributed to Koeber, Schoemaker, Van Haberer, Firney and Horsley. Gastro-jejunal anastomosis or Billroth II operation in various modern forms are modifications of the so-called Polya operation. The segment of jejunum and its direction, as well as the region of stomach joined thereto, vary in these different procedures. Contributors to various techniques of the Billroth II operation are Mikuliez, Hofmeister, Kronlein, Reichel, Polya, Moynihan, Finsterer, Balfour and W. J. Mayo among others.

—E. Tallant.

EXPERIMENTAL MEDICINE

ROSIN, A., AND DOLJANSKI, L.: *Pyroninophilic structure of liver cells in carbon tetrachloride poisoning.* (*Proceed. Soc. Exper. Biol. Med.*, v. 62, p. 62, May 1, 1946.)

The hepatic cells contain a peculiar type of granulation, which because of staining characteristics are referred to as pyroninophilic granules. In fasting animals or animals kept on a fat or carbohydrate diet the granules disappear while in animals on a high protein diet the granules are numerous. Change in size and number of the granules are an indication of disturbed protein metabolism.

One hour after administration of carbon tetrachloride the granules begin to disappear completely from the hepatic cells in the center of the lobules. This may indicate how early after carbon tetrachloride poisoning alteration in protein metabolism begins.

—M. H. F. Friedman.

Authors' Index for Volume Thirteen

Bank, Joseph	344	Mirsky, I. Arthur	130
Barry, Eileen	160	Mittelman-Galambos, Wilhelmina	14, 87, 193
Bauman, Louis	140	Morrison, Lester M.	196
Best, Charles H.	148, 155	Mosenthal, Herman O.	160
Borak, J.	249	Muehsam, Eduard	3
Braun, Imre	234	Mulsow, Frederick W.	39
Cantor, Alfred J.	247	Nasio, Juan	252
Caul, Jean	228	Necheles, H.	346
Chapman, George H.	105	Pearce, Alexander E.	344
Cromar, C. D. L.	230	Peters, John P.	127
Dallos, Arthur	279	Reed, John A.	379
Delario, A. J.	260	Roffo, Angel H.	33
Ditmore, David C.	391	Root, Howard F.	173
Ehrmann, Rudolf	23, 25	Rossien, A. X.	290
Ellenberg, Max	356	Ruskin, Simon L.	110, 311
Ershoff, B. H.	385	Sahyun, Melville	59
Feinblatt, Henry M.	386	Saltzman, A.	275, 341
Felsenfeld, Oscar	232	Sandweiss, D. J.	108
Ferguson, Edgar A., Jr.	386	Schepers, G. W. H.	333
Fisher, Ralph Lee	361	Schneck, Jerome M.	257
Friedman, M. H. F.	108	Schutz, Paul Jeffrey	299
Galambos, Arnold	14, 87, 193	Seley, Samson A.	237
Gauss, Harry	73, 213, 373	Sieve, Benjamin F.	80
Gilmore, John H.	344	Sindoni, Anthony, Jr.	178
Goldzieher, Max A.	40	Smith, Beverly Chew	138
Golob, Meyer	17, 352	Smith, Clayton S.	245
Goodman, Joseph I.	294	Snapper, I.	275, 341
Granet, Emil	330	Soper, Horace W.	350
Greenspan, E.	275, 341	Sorter, H.	346
Haist, R. E.	152	Southard, Martha E.	245
Hanes, William J.	199	Standard, Samuel	320
Hayward, Malcolm L.	255	Stiles, Karl A.	39
Hoelzel, Frederick	284	Streicher, Michael H.	1
Hoffman, Warren R.	228	Turnbull, John A.	9
Juda, A.	296	Weinberg, B. J.	346
Lasher, Earl Parsons, Jr.	221	Weinstein, L. J.	373
Long, Leonard	375	Weiss, Morris	375
Lundsteen, Erling	377	Wikoff, Helen L.	228, 245
Mascarenhas, Clovis Cruz	173	Wilensky, Abraham O.	367
McKenney, James A.	78	Young, Viola Mae	232
McKittrick, Leland S.	142	Zukerman, Morris	361
McWilliams, H. B.	385		

General Index for Volume Thirteen

Abdominal pain	299	Chewing gum	245
Abscess, appendiceal	279	Chloride	273
Achlorhydria	379	Choline	103, 123
Acne	12	Chylangioma	103
Adenylic nucleotide	311	Cirrhosis, of liver	367
Adrenaline	126	Clinical research	350
Alcohol	381	Coccygodynia	330
Allergy	9	Colitis	55, 373
Allyl bromide	386	mucous	213
Aluminum aminoacetate	31	toxic	373
Amino acids	110, 125, 212	ulcerative	252
Amoebiasis	356	Colon, diverticula of	14
Anemia	383	redundancy of	87
hemolytic	29	Constipation	1, 78, 350
nutritional	59	Continuous drip	252
Anesthesia	340	Cylindroma	55
Anoxia	310	Dermoid cyst	309
Appendicitis	39, 104, 211, 273	Dextri-maltose	29
Appetite	45, 385	Diabetes, insulin treated	193
Arterial spasm	125	mellitus	127
Atmospheric pressure	310	uncontrolled	173
Atresia, of esophagus	212	Diabetic acidosis	127
Avitaminosis	309	Diaphragmatic pain	303
Azotemia	28	Diarrhea	58, 196
		European	199
		Diets, high lipid	228
Bacteriophage	274	Disorders, gastrointestinal	255
Banti's syndrome	361	Diverticula, of colon	14
Barbiturates	104	Duodenal ulcer	389
Basal metabolism	45	Duodenitis	310
B complex vitamins	110	Dysentery, amebic	272
Benadryl	123	bacillary	212
Benzoic acid	275, 341	Dyspepsia	350
Bilirubin	27, 31, 340		10
Blood sugar, postprandial	178	Eczema	61
Blood sugar tests	160	Edema	126
Boils	13	Egg white	23
Brucellosis	103	Ehrmann meal	228
		Elimination, intestinal	351
		Enema	351
Calcium	274	Enteritis	346
Cancer, gastric	17	regional	105
gastrointestinal	25	Enterococci	126
jejunal	234	Enzymes, proteolytic	55
of esophagus	55, 249	Epithelioma	124
of stomach	104, 379	Erosions, chick gizzard	12
Carbohydrate metabolism	152	Erythema	375
tolerance	193	Esophageal spasm	130
Carbon tetrachloride	124	Etiology, of diabetes	23
Carcinogenesis	33	Ewald meal	
Cardiospasm	352, 377		

Fasting blood sugar	178	Intestinal absorption	104
contents	284	Intussusception	26
Fat	49	Iron	57
Fats	124		
Fat transport	155	Laboratory tests, of stomach	23
Fissure	391	Lactic acid	340
Food rationing	29	Laxatives	386
		Lead	126
Gall stones	14, 101	poisoning	306
Gangrene, in diabetics	142	Lesions, of cardia	124
Gastragogue	386	Lipase	30
Gastrectomy	27, 56, 123, 310	Lipophilia	48
Gastric acidity	245	Liver changes	309
cancer	56, 310	cirrhosis of	57
contents	31, 284	extract	58
diagnosis	290	fat	340
function	284	function test	212
resection	28	lipase	309
retention	57	regenerating	30
secretion	108, 340	trauma	309
ulcer	380	Lymphoblastoma	273
Gastritis	26, 360	Lymphoma	211
atrophic	273		
hypertrophic	344	Measles	211
Gastrosocopy	103, 290	Medical research	148
G. I. symptoms, in schizophrenia	257	Megacolon	3
Glucose, in coma	170	Microorganisms, enteric	232
Glucuronates	275, 341	Modified globin	274
Glycerides, unsaturated	228	Mucous colitis	213
Glycogen	31	Mucus secretion	57
Gros reaction	340	Muscle metabolism	110
		spasm	311
HCl	126		
Hematemesis	350	Nasal ganglion	311
Hemoglobin	324	Necrosis, diatetic	104
Hemorrhoidectomy	104	Neoplasm	344
Hepatic disease	56	Neuropathy, in diabetes	173
function test	58	Nicotinamide	58
Hepatitis	27, 103, 272, 273, 294, 340, 361	Nicotinic acid	125
Hepatoma	28	Nitrogen	309
Hippuric acid	275		
Hirschsprung's disease	3	Obesity	40
Histamine	309	Obstruction, of pylorus	238
test	23	Oils, oxidated	33
Hormones	80, 323		
Hyperplasia, of stomach	57	Pain, abdominal	73
Hyperthyroidism	306	arthritic	311
Hypoproteinemia	59	Pancreatectomy	211
		Penicillin	359
Icterus	123, 271	Peptic ulcer	221, 260, 308, 351
Ilcitis	321	Peptidase	310
regional	352	Percussion of liver	294
Indicanuria	350	Perianal dyscrasia	330
Insulin	185	Peritoneal pain	301

Phospholipid	125
Physiological derangements	320
Plummer's dilator	377
Pneumonia	73
Polyn neuritis	310
Polysaccharides	385
Porphyria	309
Proctalgia	330
Proctology	247
Prolapsus recti	56
Protein deficiency	59
Prothrombin	57
Protozoa, intestinal	232
Pruritus	11
ani	330
Psoriasis	13
Psychotherapy	255
Pyelitis	310
Pyrosis	333
Radiation therapy	249
Rectal incontinence	296
Saliva	310
Schizophrenia	257
Scurvy	30
Segmental neuralgia	302
Shock	152
Sigmoidoscopy	351
Sodium benzoate	275
Specific dynamic action	46
Splenic puncture	274
tumor	274
Stomach, cancer of	17
tests of	23

Streptococci, fecal	105
Succinylsulfathiazole	37
Sulfadiazine	358
Sulfonamide	373
Surgery, in diabetics	138
Sympathetic block	311
Syphilis	305, 352
Thiamine	175
deficiency	29
Tomato pomace	196
Triolein	228
Tuberculin	273
Typhoid fever	31, 273, 274
Tyrothricin	247
Ulcer	27
intestinal	28
of cecum	230
peptic	238
Ulcerative colitis	346
Undernutrition	29
Urticaria	11
Vitamin A	55, 125, 323
B	212
deficiency	30
K	28
synthetic	351
Vitamins	80
Water	78
retention	50
Yeast, brewers	272

